RECENT ADVANCES IN ORGANIC CHEMISTRY

by

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AND

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PUBLISHER'S NOTE

Volume I, which can no longer be regarded as dealing with *recent* advances in organic chemistry and is therefore mainly of historical interest, is now out of print.

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PREFACE

THIS edition — the seventh — of *Recent Advances in Organic Chemistry*, on account of the many interesting and important developments in Organic Chemistry, has been re-arranged as Volumes II and III of the series.

In each volume the sections have been revised and extended to include new work, and in the cases of the polysaccharides, diterpene and triterpene compounds, where advances have been very rapid, a separate chapter has been given to each of these three groups. New chapters on Pectic Substances and Alginic Acid, Lignans, Porphyrins, Azaporphyrins, Synthetic High Polymers and Condensates, Deutero-Organic Compounds, and Some Aspects of Stereochemistry have been added. Inspection of the tables of contents will show how these topics have been arranged in the two volumes.

The references to the literature are indicated by figures, whilst footnotes are distinguished by asterisks. In the index of each volume the principal reference is in heavier type.

The two books will, it is hoped, serve to guide the reader in the fields with which they deal, and encourage him to go further in the study of the various subjects discussed, since this is the main function of a work of this kind.

In preparing these volumes I was fortunate in having the advice and counsel of Professor A. W. Stewart before his untimely death in June 1947.

In conclusion I desire to acknowledge the great assistance which has been given to me by Dr. R. C. Pink, who undertook the onerous task of proof-reading, and I am further indebted to him for many helpful suggestions, which have led to improvements in the text.

HUGH GRAHAM.

The Queen's University of Belfast,
March 1948.

HALF-TONE PLATES

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II SPACE-MODELS SHOWING THE ISOMERISM IN REDUCED NAPHTHALENE RINGS 234

RECENT ADVANCES IN ORGANIC CHEMISTRY

CHAPTER I

THE BILE ACIDS AND STEROLS

A.—INTRODUCTORY

THE organic acids which occur in animal bile are usually present in the form of sodium salts of the amides with glycine and taurine. For example, sodium glycocholate has the formula $C_{23}H_{36}(OH)_3CONHCH_2COONa$. The best known and those acids which have been subjected to considerable chemical examination are :—

Acid	Formula	Position of OH groups at C-atom
I. Mono-hydroxycholanic Group,	$C_{23}H_{38}.(OH).COOH$	
1. Lithocholic.		3.
II. Di-hydroxycholanic Group,	$C_{23}H_{37}(OH)_2.COOH$	
1. Deoxycholic.		3, 12.
2. Hyodeoxycholic.		3, 6.
3. Chenodeoxycholic.		3, 7.
III. Tri-hydroxycholanic Group,	$C_{23}H_{36}(OH)_3.COOH$	
1. Cholic.		3, 7, 12.
2. β-Phooeacholic.		3, 7, 23.

There is a very close structural relationship between the known bile acids and sterols. The sterols are widely distributed in the animal and vegetable kingdoms. Cholesterol is present in many parts of the human organism including the bile, brain.

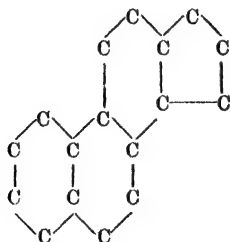
blood, liver and kidneys. The fact that cholesterol is one of the principal constituents of gall-stones makes it of prime medical importance. Cholesterol is also found in many oils, fats and waxes and in egg yolk. In the human body it is present both free and combined with higher fatty acids. Ergosterol is found in relatively small quantities associated with cholesterol, and may also be obtained from yeast and ergot. On irradiation with ultra-violet light under suitable conditions ergosterol is converted into vitamin D. Both cholesterol and ergosterol are unsaturated alcohols.

The most important sterols are :

Sterol	Formula	Number of double bonds
Coprosterol (Coprostanol) . .	$C_{27}H_{47}.OH$	0
Cholesterol	$C_{27}H_{45}.OH$	1
Ergosterol	$C_{28}H_{43}.OH$	3
Stigmasterol	$C_{29}H_{47}.OH$	2

Other bile acids and sterols are known, but have not been examined chemically in any detail.

Great impetus was given to the elucidation of the constitutions of the bile acids, sterols and related compounds by the suggestion of Rosenheim and King[1] that the ring system of these compounds is the cyclopenteno-phenanthrene skeleton,

```
              C     C
            /   \ /   \
           C     C     C
           |     |     |
           |     C-----C
      C     C   /
    /   \ /   \/
   C     C     C
   |     |     |
   C     C     C
    \   / \   /
      C     C
```

The bile acids and sterols may be regarded as derivatives of the hydrocarbon cholane, $C_{24}H_{42}$ (I.).

The parent acid is known as cholanic acid (II.).

[1] Rosenheim and King, *J.S.C.I.*, **51** (1932), 464, 954.

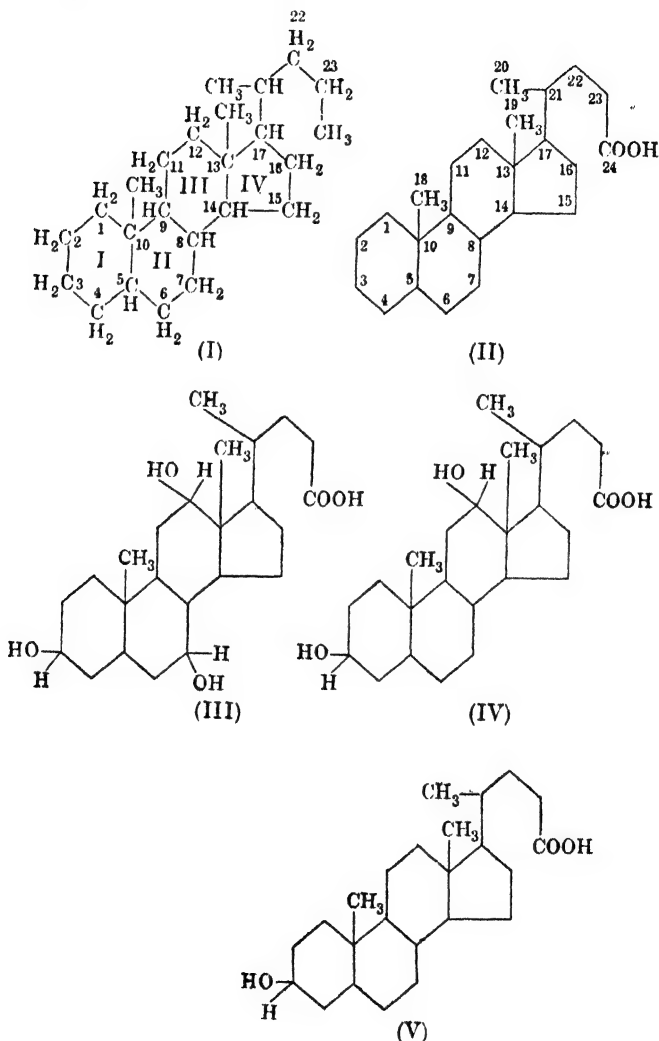
Cholic acid is 3 : 7 : 12-tri-hydroxycholanic acid (III.), deoxycholic acid is 3 : 12-di-hydroxycholanic acid (IV.), and lithocholic acid is 3-hydroxycholanic acid (V.).

(I)

(II)

(III)

(IV)

(V)

The prefix "*allo*" is used to denote the saturated bile acid derivatives in which the steric configuration of rings I. and II. corresponds to *trans*-decalin, e.g. *allo*cholanic acid, *allonor*cholanic

acid and 3-hydroxy*allo*cholanic acid. The corresponding acids of the *cis*-series are cholanic acid, *nor*cholanic acid and 3-hydroxycholanic acid. In coprostanol and the bile acids rings I. and II. are in the *cis*-position, whereas in cholestanol and its derivatives they are in the *trans*-position.

By analogy with epimerisation in the aldoses, when isomerism in the cholane compounds is due to steric inversion of an hydroxyl group the prefix " *epi* " is employed.

Thus *epi*cholestanol is the epimeride of cholestanol

In the sterols the following systematic nomenclature has been adopted. The word sterol is reserved for the naturally occurring compound, for example, cholesterol and ergosterol.

If the compound is a *saturated alcohol* the name ends in " stanol," e.g., cholestanol, ergostanol.

If the compound is an *unsaturated alcohol* the name ends in " stenol," e.g., cholestenol, coprostenol.

If the compound is a *saturated ketone* the name ends in " stanone," e.g., cholestanone, coprostanone.

If the compound is an *unsaturated ketone* the name ends in " stenone," e.g., coprostenone.

If the compound is a *saturated hydrocarbon* the name ends in " stane," e.g., coprostane, cholestane.

If the compound is an *unsaturated hydrocarbon* the name ends in "stene," e.g., coprostene, cholestene.

As the naturally occurring coprosterol is saturated it has been suggested that the name should be changed to coprostanol.[1]

The nomenclature is shown in tabular form below.

STEROLS

If an—	Saturated	Unsaturated	
Alcohol . .	-stanol	-stenol	Name ends in
Ketone . .	-stanone	-stenone	
Hydrocarbon .	-stane	-stene	

[1] Rosenheim and King, *J.S.C.I.* (1934), **53**, **91**.

B.—The Structural Relationship of the Bile Acids to the Sterols

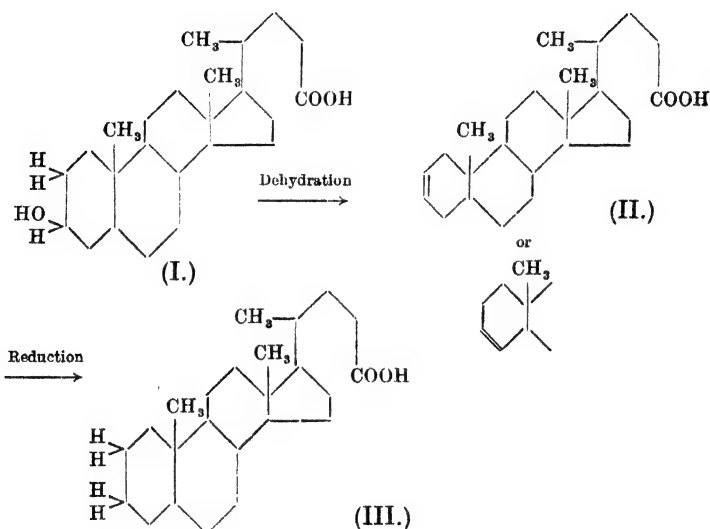
On vacuum distillation, lithocholic acid (I.) splits off its hydroxyl group by dehydration with the formation of cholenic acid (II.). This unsaturated acid on catalytic reduction is converted into cholanic acid (III.).[1]

CH_3 CH_3 COOH CH_3 H H HO H (I.)

Dehydration →

CH_3 CH_3 COOH CH_3 (II.) or CH_3

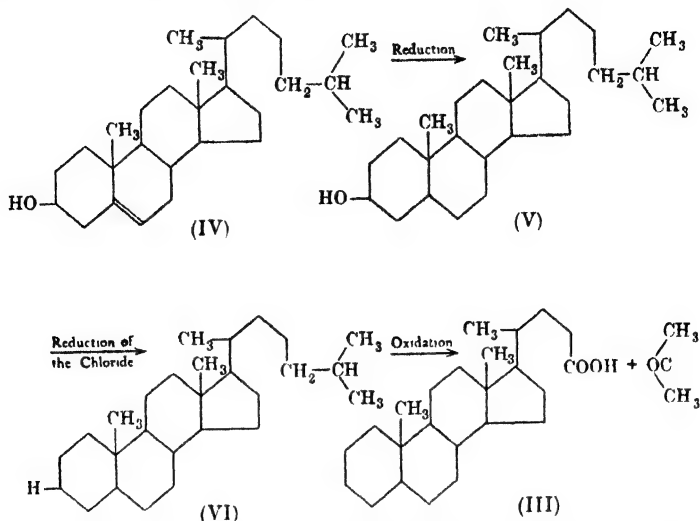
Reduction →

CH_3 CH_3 COOH CH_3 H H H H (III.)

Cholesterol (IV.), on reduction, yields coprosterol (V.), which on reduction through its chloride gives rise to the corresponding saturated hydrocarbon coprostane (VI.). An *iso*propyl group, in the form of acetone, can be split off the coprostane molecule by oxidation with chromic acid producing the same cholanic acid (III.).[2]

[1] Wieland and Weil, *Z. physiol. Chem.*, 1912, **80**, 287; Wieland and Sorge, *ibid.*, 1916, **98**, 59; Wieland and Weyland, *ibid.*, 1920, **110**, 123; Windaus, Bohne and Swarzkopf, *ibid.*, 1924, **140**, 177; Windaus, *Annalen*, 1926, **447**, 223.

[2] Windaus and Neukirchen, *Ber.*, 1919, **52**, [B], 1915.

(IV) —Reduction→ (V)

—Reduction of the Chloride→ (VI) —Oxidation→ (III) COOH + OC$(CH_3)_2$

Many degradations of the sterols result in compounds identical with those obtained by the breakdown of bile acid derivatives, and leave no doubt that the major portions of the molecular frameworks of the two series of compounds are the same.

C.—The Carbon Framework of the Bile Acids and Sterols

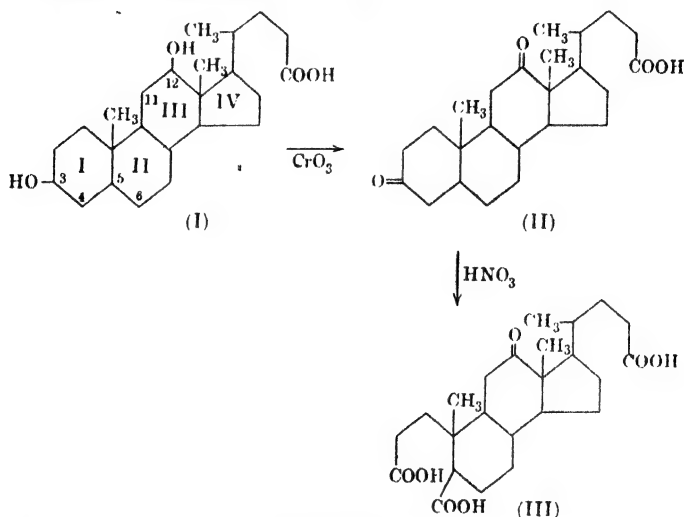
1. *Some Decomposition Products*

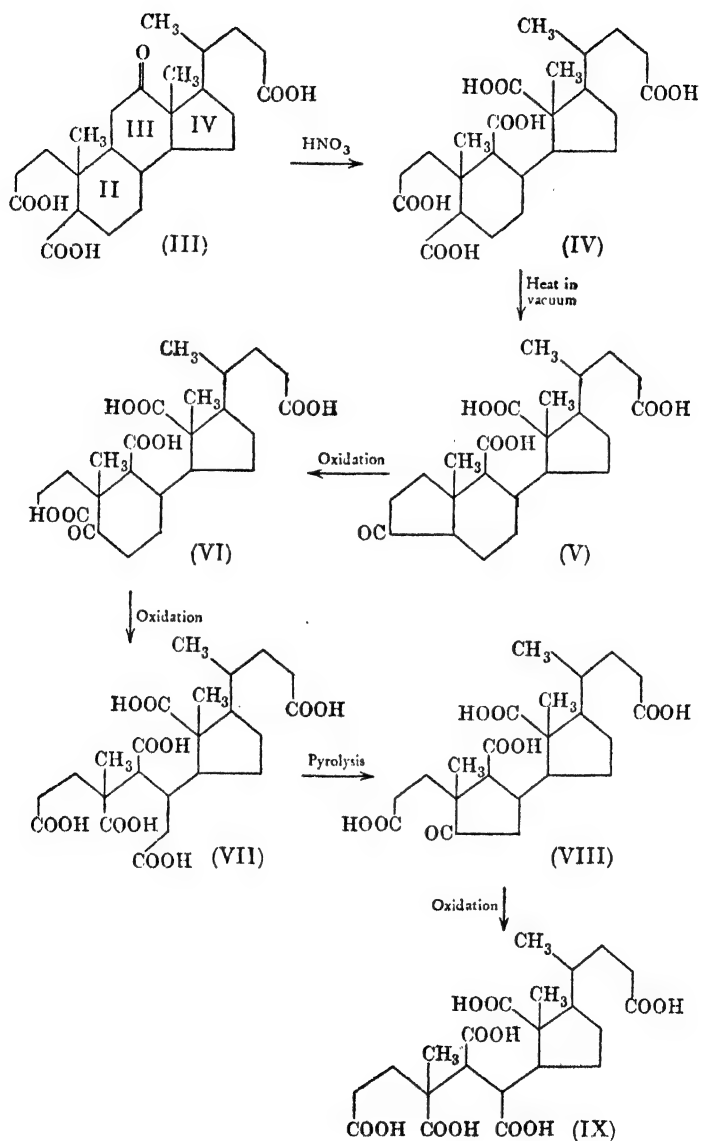
Consideration of the graphic formula assigned to any bile acid or sterol shows that before this can be taken as correct, proof must be forthcoming, (*a*) of the structure of the ring system, (*b*) of the structure of the side-chain, (*c*) of the point of attachment of the side-chain to the ring system, (*d*) of the presence and points of attachment of the methyl groups to the ring system, (*e*) of the points of attachment of the hydroxyl groups, (*f*) of the positions of the double carbon bonds (sterols). In addition, the nature of the isomerism involved must be elucidated. Finally the compounds must be synthesized by steps from simpler compounds of known constitution. These criteria have to an extent been satisfied.

The different steps in the degradation of the bile acids have been explained very successfully on the assumption that the compounds have the structures assigned to them by Rosenheim and King. The bile acids tabulated on page 1 can all be converted into cholanic acid by dehydration to unsaturated acids

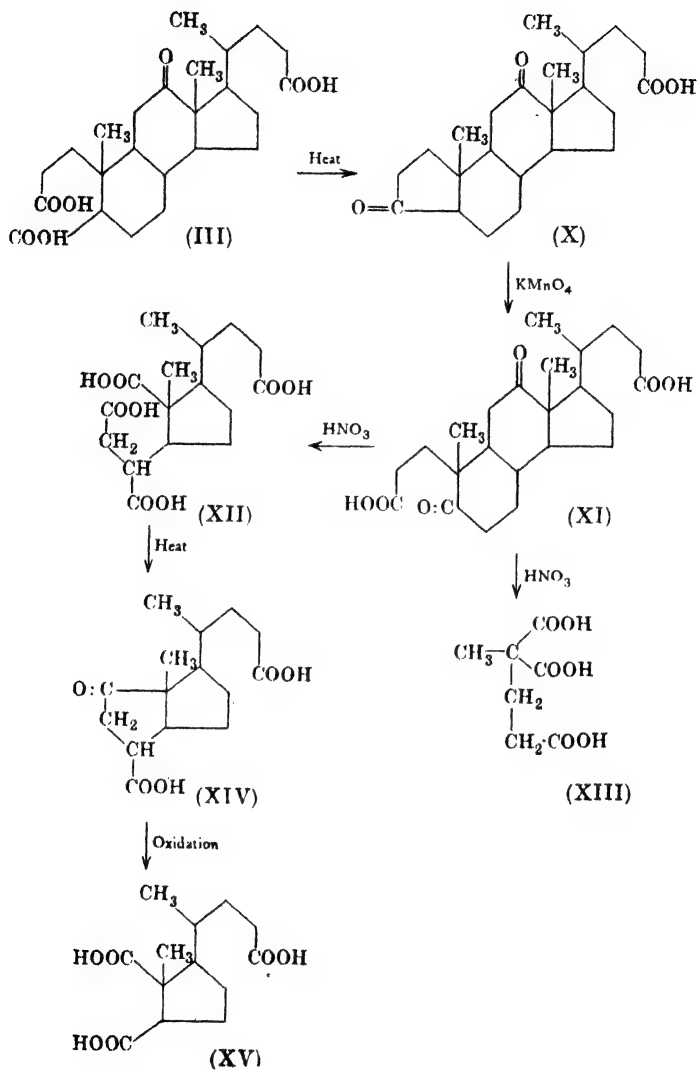
followed by catalytic reduction.[1] These steps have been illustrated on page 5 in the case of lithocholic acid.

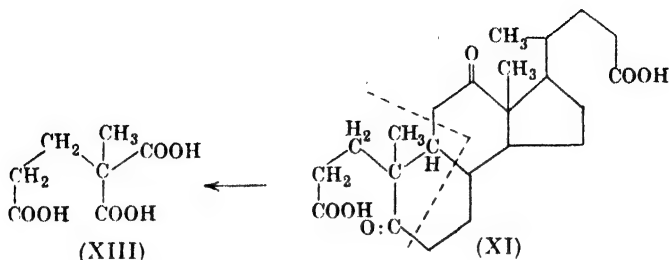
All the bile acids on oxidation with chromic acid yield the corresponding keto-acids. For example, deoxycholic acid (I.) yields the di-ketocholanic acid (dehydrodeoxycholic acid) (II.), and cholic acid yields the tri-ketocholanic acid (dehydrocholic acid). These keto-acids, on further regulated oxidation by rupture of ring I. at the point C_3–C_4, give rise to tricarboxylic acids. The diagram below illustrates the conversion of deoxycholic acid (I.) into deoxybilianic acid (III.),[2]

(I) —CrO_3→ (II) —HNO_3→ (III)

When deoxybilianic acid (III.) is further oxidized with nitric acid choloidanic acid (IV.) is produced by fission of ring III. at the point C_{11}–C_{12}. When this penta-acid is heated in a vacuum it splits off carbon dioxide and water, yielding pyrocholoidanic acid (V.). Further oxidation produces prosolanellic acid (VI.), which can be converted into solanellic acid (VII.) by the oxidative rupture of ring II. at the point C_5–C_6. Pyrolysis converts solanellic acid into pyrosolanellic acid (VIII.), containing a new 5-membered ring. Oxidation of the pyro-acid gives rise to biloidanic acid (IX.),which has been shown to be a hexa-acid derivative of cyclopentane. These changes may be represented as follows :[3]

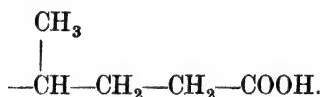
[1] Wieland and Weil, *Z. physiol. Chem.*, 1912, **80**, 287.
[2] Wieland and Kulenkampff, *ibid.*, 1920, **108**, 295.
[3] Wieland and Schulenberg, *ibid.*, 1922, **126**, 232.

Cholic acid also yields biloidanic acid (IX.) on similar treatment. This shows the connection between deoxycholic acid and cholic acid. The above series of changes indicates the positions occupied by the hydroxyl groups of deoxycholic acid. If formula (IV.) be correct, it is obvious that the two first places of oxidative attack are at the points occupied by the hydroxyl groups in the original acid.

If, alternatively, deoxybilianic acid (III.) is heated in a vacuum it is converted into pyrodeoxybilianic acid (X.). Oxidation of this compound with potassium permanganate gives rise to a diketo dibasic acid (XI.), which on oxidation with nitric acid yields a tetrabasic acid (XII.), and *n*-butane $\alpha\gamma\gamma$-tricarboxylic acid (XIII.). The acid (XII.) when heated produces a keto-dibasic acid (XIV.) which can be oxidized to a tribasic acid (XV.) which was identified as a cyclopentane derivative.[1] These degradations can be formulated as follows :

[1] Wieland and Vocke, *Z. physiol. Chem.*, 1928, **177**, 68.

The formation of *n*-butane αγγ-tricarboxylic acid (XIII.) which contains a tertiary carbon grouping from compound (XI.) may arise as follows :

(XIII) ⟵ (XI)

and may be taken as evidence of the presence of a methyl group in position C_{10} of the bile acid compounds.

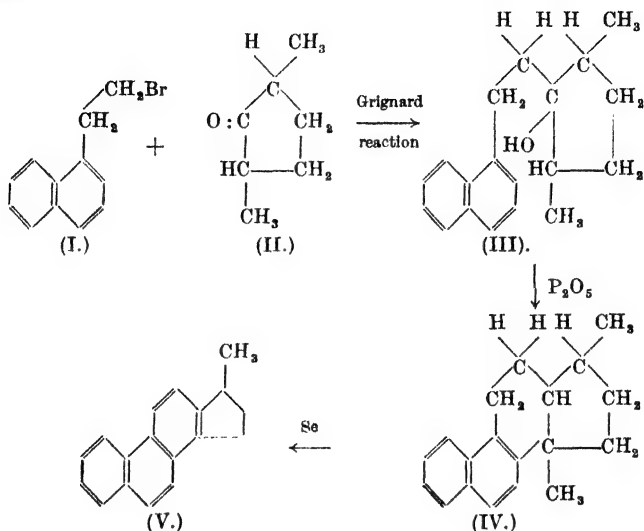
Compound (XII.), on examination, was proved to be a tetrabasic acid and to contain one cyclopentane ring,[1] and the side-chain shown to contain five carbon atoms in the form of

$$\begin{array}{l} CH_3 \\ | \\ \!\!-CH-CH_2-CH_2-COOH. \end{array}$$

2. *The Synthesis of* 3′-*methyl*-1 : 2-*cyclopentenophenanthrene*

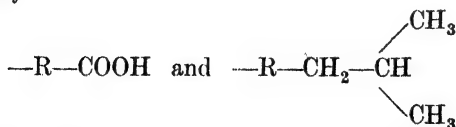
The structure of the ring system of the bile acids and sterols has been confirmed by the synthesis of 3′-methyl-1 : 2-cyclopentenophenanthrene and the identity of this compound with Diels's Hydrocarbon, $C_{18}H_{16}$ shown.[2] Both cholesterol and ergosterol on dehydrogenation with selenium yield the hydrocarbon, $C_{18}H_{16}$. This compound has been synthesized as follows, β(α-naphthyl) ethyl bromide (I.) was condensed with 2 : 5-dimethyl cyclopentanone (II.) by means of the Grignard reaction with the production of 2 : 5-dimethyl-1-β-(α-naphthyl) ethylcyclopentanol (III.). The alcohol (III.) when heated with phosphorus pentoxide under reduced pressure yielded 1 : 3-dimethyl-1 : 2-cyclopentano-1 : 2 : 3 : 4-tetrahydrophenanthrene (IV.). From the hydrocarbon (IV.) by dehydrogenation with

[1] Wieland and Schlichting, *Z. physiol. Chem.*, 1924, **134**, 276.
[2] Harper, Kon and Ruzicka, *J.*, 1934, 124.

selenium 3′-methyl-1 : cyclopentenophenanthrene (V.) was isolated. The steps in the synthesis are shown diagrammatically below.

(I.) + (II.) —Grignard reaction→ (III). —P_2O_5→ (IV.) —Se→ (V.)

3. *The Side Chains of the Bile Acids and Sterols*

(*a*) *The Structure.*—One of the principal differences between the bile acids and sterols is in the nature and dimensions of the side-chains. Cholesterol, on oxidation, splits off acetone, the bile acids do not give the ketone under similar treatment.[1] As has been already pointed out, coprostane, a derivative of cholesterol, when it loses a molecule of acetone by oxidation, is converted into cholanic acid. The two side chains are presumably :

$$\text{—R—COOH} \quad \text{and} \quad \text{—R—CH}_2\text{—CH}\begin{matrix}\diagup CH_3 \\ \diagdown CH_3\end{matrix}$$

The structure of the side-chain in cholanic acid has been demonstrated by alternate Grignard condensations and oxidations with chromic acid.[2] By this means the chain was shortened one carbon atom at a time until it was completely removed.

[1] Windaus and Neukirchen, *Ber.*, 1919, **52**, [B], 1915.
[2] Wieland, Schlichting and Jacobi, *Z. physiol. Chem.*, 1926, **161**, 180.

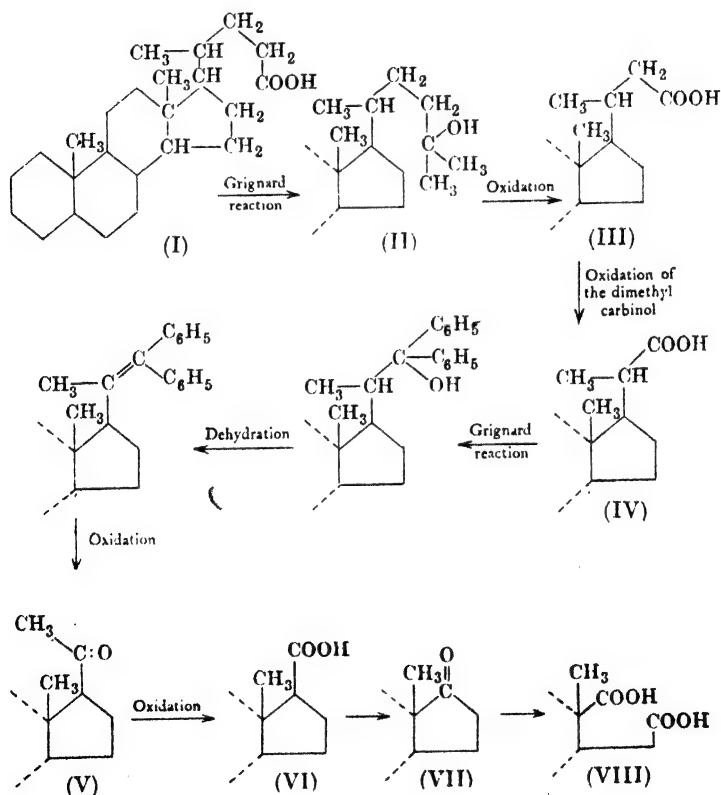
Cholanic acid (I.) was converted into the dimethyl carbinol (II.) and oxidized to *nor*cholanic acid (III.). These steps were repeated with the formation of *bisnor*cholanic acid (IV.). This acid was converted into the diphenyl carbinol, which was dehydrated and then oxidized to ætiocholylmethylketone (V.). Oxidation of the ketone produced ætiocholanic acid (VI.), and then the last carbon atom of the chain was eliminated with the formation of ætiocholanone (VII.). Further treatment resulted in the production of ætiobilianic acid (VIII.) by rupture of the cyclopentane ring. The diagram shows these different steps.

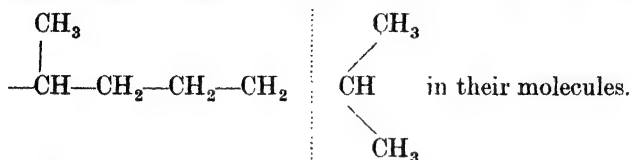
(I) Grignard reaction (II) Oxidation (III)

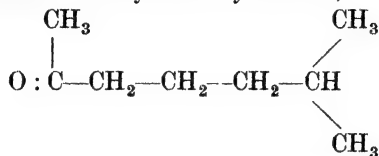
Oxidation of the dimethyl carbinol

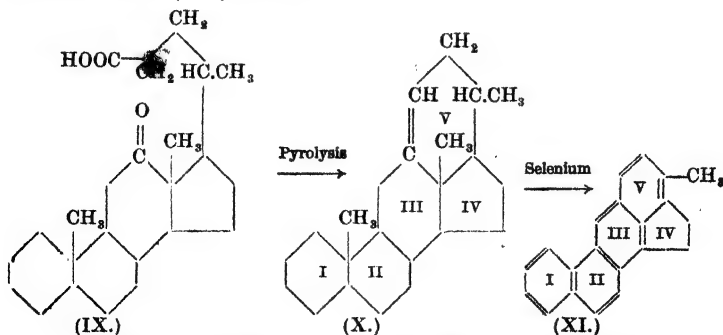
(IV) Grignard reaction — Dehydration

Oxidation

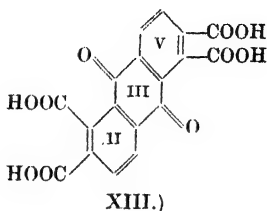
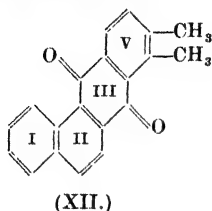
(V) Oxidation (VI) → (VII) → (VIII)

Consequently the compounds, such as lithocholic, deoxycholic and cholic acids, related to cholanic acid, have also this side chain structure in the molecule. It follows from the conversion of coprostane into cholanic acid by the loss of an isopropyl group that it and its related compounds have the side-chain

$$\begin{array}{l} CH_3 \\ | \\ -CH-CH_2-CH_2-CH_2 \end{array} \; \vdots \; \begin{array}{l} \quad CH_3 \\ \;\; / \\ CH \\ \;\; \backslash \\ \quad CH_3 \end{array} \quad \text{in their molecules.}$$

The production of methyl *iso*hexyl ketone,

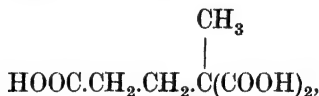
$$\begin{array}{l} \quad\;\; CH_3 \qquad\qquad\qquad\qquad\quad CH_3 \\ \quad\;\; | \qquad\qquad\qquad\qquad\qquad\;\; / \\ O : C-CH_2-CH_2-CH_2-CH \\ \qquad\qquad\qquad\qquad\qquad\qquad\;\; \backslash \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3 \end{array}$$

by oxidation of cholesteryl acetate confirms the presence of eight carbon atoms and the structure given to the coprostane side chain.[1]

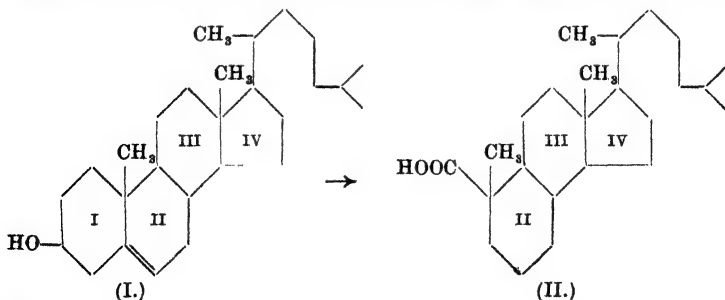
(*b*) *The position of the side-chain.*—The side-chain of the bile acids and sterols has been assigned to ring IV. at the point C_{17}. From the results obtained by degradation of the various bile acids there can be no doubt about the attachment of the side-chain to ring IV. Point C_{17} is preferred for the following reasons. Pyrolysis of 12-ketocholanic acid (IX.) gives rise to a hydrocarbon, dehydro*nor*cholene (X.).[2] When this hydrocarbon is dehydrogenated it passes into an aromatic compound methyl cholanthrene [3] (XI.) as follows :

[1] Windaus and Resan, *Ber.*, 1913, **46**, 1246.
[2] Wieland and Weidersheim, *Z. physiol. Chem.*, 1930, **186**, 229.
[3] Wieland and Dane, *ibid.*, 1933, **219**, 240.

The structure of the aromatic hydrocarbon (XI.) has been confirmed by its oxidation to 5 : 6-dimethyl-1 : 2 : benzanthraquinone (XII.) and then to anthraquinone-1 - 2 : 5 : 6-tetracarboxylic acid (XIII.).[1]

(XII.) XIII.)

4. *The Positions of the Methyl Groups in the Framework*

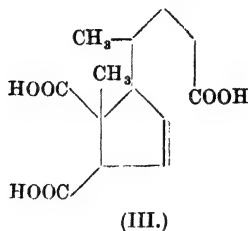
The two methyl groups have been placed at the points C_{10} and C_{13}. The formation of *n*-butane $\alpha\gamma\gamma$ tricarboxylic acid,

$$HOOC.CH_2.CH_2.C(CH_3)(COOH)_2,$$

as a decomposition product of pyrodeoxybilianic acid through its diketo-dibasic acid derivative (*see* page 9) is strong evidence in favour of C_{10} as one point of attachment of a methyl group. This view is supported by the Grignard-oxidation step-by-step degradation of ring I. in cholesterol (I.) to a monobasic acid (II.), which is presumed to have a tertiary carbon atom adjacent to the carboxyl, since the acid is esterified with difficulty.

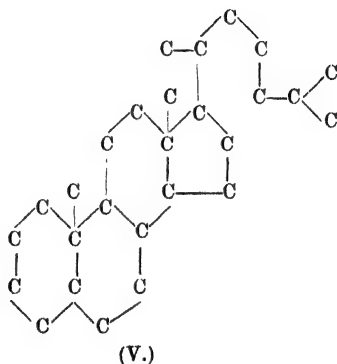
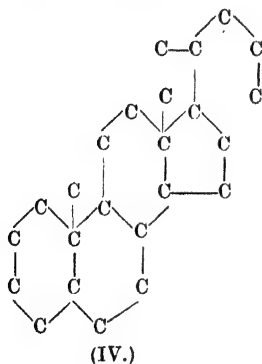
(I.) (II.)

The second methyl group has been assigned to C_{13} on account of the properties of the tribasic acid derivative of cyclopentane (III.) obtained by the degradation of deoxycholic acid.

[1] Cook, Hewitt and Haslewood, *Chem. and Ind.*, 1933, 949.

CH_3 CH_3 HOOC COOH HOOC

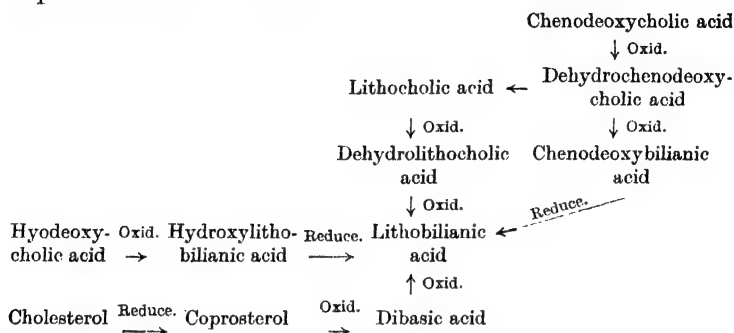
(III.)

If it be permitted to postulate the migration of a methyl group from C_{13} to C_{17} during the selenium dehydrogenation of cholesterol when 3′-methyl-1 : 2-cyclopentenophenanthrene (Diels's Hydrocarbon) is formed, this production could be taken as supporting the facts in favour of C_{13} as the point of attachment of the second methyl group.

The foregoing proofs and assumptions allow the carbon skeleton of the bile acids to be written as (IV.), and cholesterol and its relatives as (V.).

(IV.) (V.)

D.—The Positions of the Hydroxyl Groups in the Bile Acids and Sterols

Reference to the table on page 1 shows the positions allocated to the hydroxyl groups in the bile acid molecules. In each of the sterols cholesterol, coprosterol, ergosterol and stigmasterol the sole hydroxyl group has been assigned to position C_3 in ring I. If these dispositions are correct it is evident that C_3 is a key position, as in all the natural compounds under discussion it is occupied by an hydroxyl group. Provided that the

hydroxyl group of lithocholic acid can be proved to occupy position C_3 in ring I., and the relationship of this acid to the other compounds demonstrated, a considerable step forward will have been made in proving the positions of the hydroxyls in these other substances. The diagram shows some of the relationships of lithocholic acid to the other bile acids, to coprosterol and to cholesterol.

Chenodeoxycholic acid
↓ Oxid.
Lithocholic acid ← Dehydrochenodeoxycholic acid
↓ Oxid. ↓ Oxid.
Dehydrolithocholic acid   Chenodeoxybilianic acid
↓ Oxid.   Reduce.
Hyodeoxycholic acid —Oxid.→ Hydroxylithobilianic acid —Reduce.→ Lithobilianic acid ←
↑ Oxid.
Cholesterol —Reduce.→ Coprosterol —Oxid.→ Dibasic acid

Cholesterol (I.), on reduction, can be converted into coprosterol (II.) which retains the alcoholic properties of cholesterol, and presumably has its hydroxyl group in the same position in the molecule. Coprosterol (II.), on oxidation, yields a dibasic acid (III.) with no alcoholic properties. The dibasic acid, on further oxidation, splits off a molecule of acetone with the formation of the tribasic acid, lithobilianic acid (IV.), which is also obtained from lithocholic acid by oxidation. The changes may be represented as follows :

CH$_2$ CH$_3$—CH CH$_2$ CH$_3$ CH$_3$ CH$_2$—CH CH$_3$ CH$_3$ HO (I)

Reduce →

HO (II)

↓ Oxidise

COOH HOOC HOOC (IV)

← Oxidise

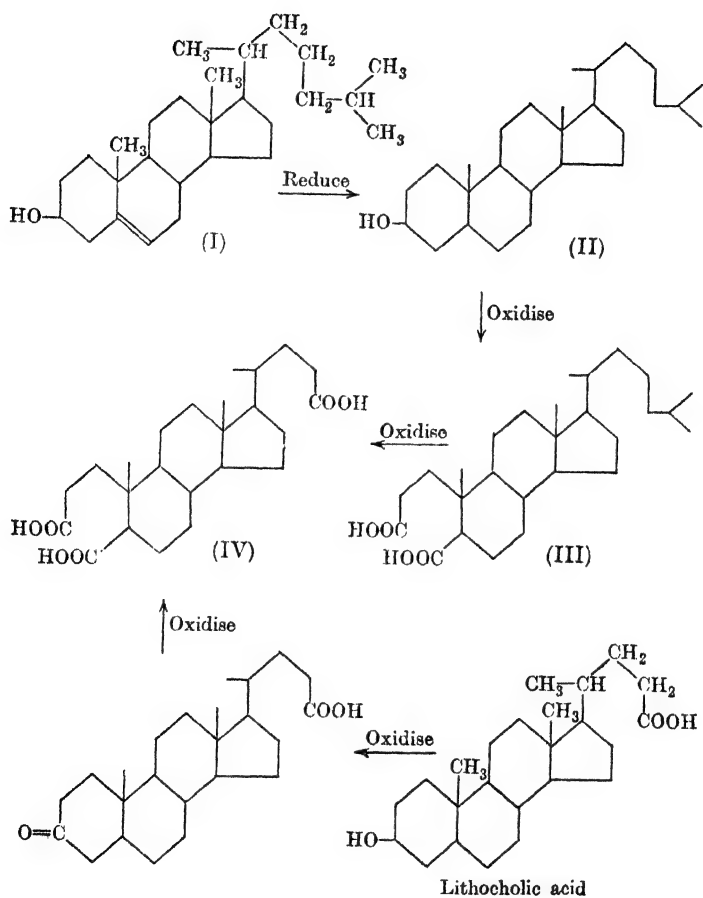
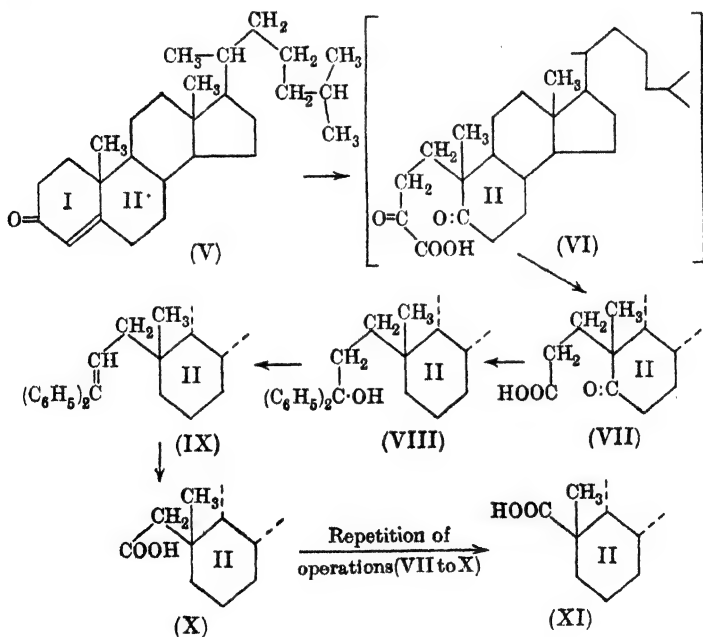
HOOC HOOC (III)

↑ Oxidise

COOH O=C

← Oxidise

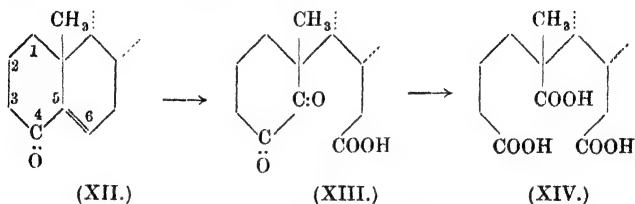
CH$_2$ CH$_3$—CH CH$_2$ CH$_3$ COOH CH$_3$ HO

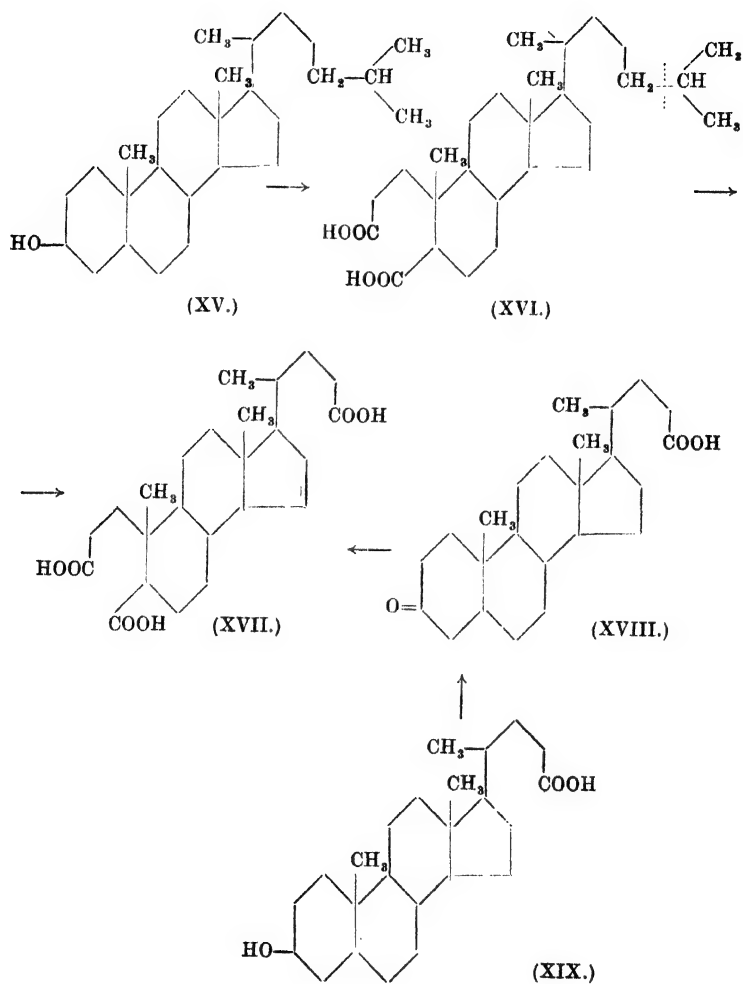
Lithocholic acid

Cholesterol, on oxidation, was converted into the ketone, cholestenone (V.), which has been shown to be unsaturated in the αβ position relative to the carbonyl group.[1] The ketone, on further oxidation, yielded a monobasic monoketonic acid (VII.), probably through the diketonic acid (VI.). This acid, after reduction and esterification, was treated with phenyl magnesium bromide with the production of the diphenyl carbinol (VIII.). Dehydration of the carbinol yielded an unsaturated hydrocarbon (IX.). The action of ozone followed by chromic acid converted the hydrocarbon into the lower relative (X.) of the acid (VII.). These steps were repeated with the formation of the next lower acid (XI.). Thus two carbon atoms were eliminated from the chain attacked, and an acid obtained as the end product.[2] These changes are formulated in the diagram below.

Taking the combined facts into account, it is evident that the ketonic group of cholestenone is in position C_3. From

[1] Menschick, Page and Bossert, *Annalen*, 1932, **495**, 225; Bonstedt, *Z. physiol. Chem.*, 1933, **214**, 173.

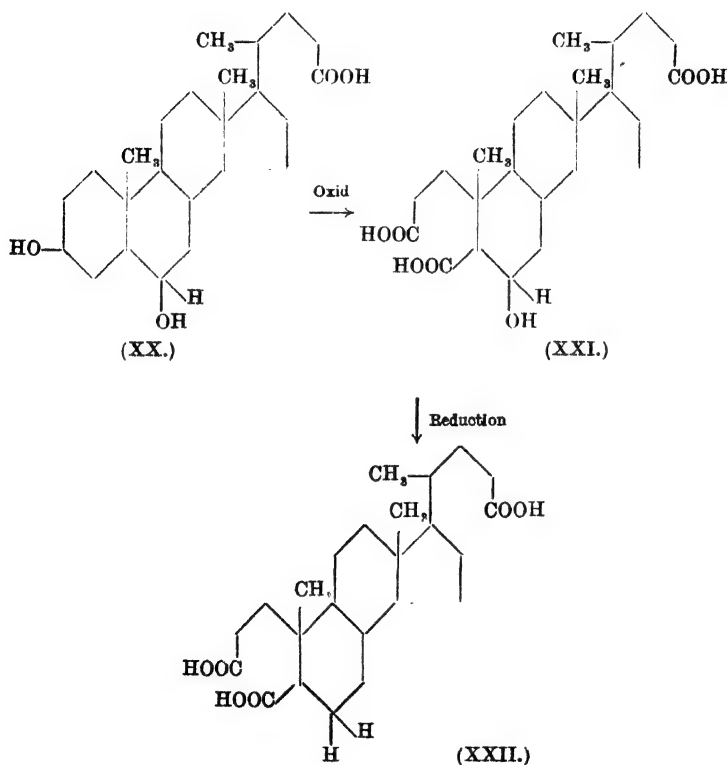
[2] Tschesche, *Annalen*, 1932, **498**, 185.

inspection of the other possible formulæ of cholestenone as an αβ unsaturated ketone, it is apparent that the oxidation to acid (VII.) involving the elimination of one carbon atom from the molecule could not take place. For example, if the double bond were in position C_5–C_6 and the carbonyl group at point C_4 (XII.), oxidation could not give rise to a monoketo-monobasic acid such as (VII.), but would probably yield the tribasic acid (XIV.) without loss of carbon.

(XII.) (XIII.) (XIV.)

Similarly position C_3–C_4 for the double bond and point C_2 for the ketonic group may be rejected. The step-by-step degradation of the keto acid (VII.) shows that the hydroxyl group of the parent substance cholesterol must have been in ring I. and at point C_3.

From the relationship, cholesterol → coprosterol (XV.) → dibasic acid (XVI.) → lithobilianic acid (XVII.) on the one hand, and the connection, lithocholic acid (XIX.) → dehydrolithocholic acid (XVIII.) → lithobilianic acid (XVII.) on the other, it follows that lithocholic acid has its hydroxyl group in the same ring and also in position C_3. The changes from coprosterol (XV.) to lithobilianic acid (XVII.) may be represented as taking place by the opening of ring I. at the point of attachment of the hydroxyl group, and the splitting off of an isopropyl group from the side-chain.

A few other examples will be sufficient to illustrate the methods by which the hydroxyl groups of the bile acids and sterols have been allocated. Hyodeoxycholic acid (XX.), on careful oxidation with hypobromite, yields a lithobilianic acid derivative, hydroxylithobilianic acid (XXI.). On reduction, lithobilianic acid (XXII.) is formed. Therefore hyodeoxycholic acid has one hydroxyl group in ring I. at the point C_3. These changes may be represented as,

(XX.) —Oxid→ (XXI.)

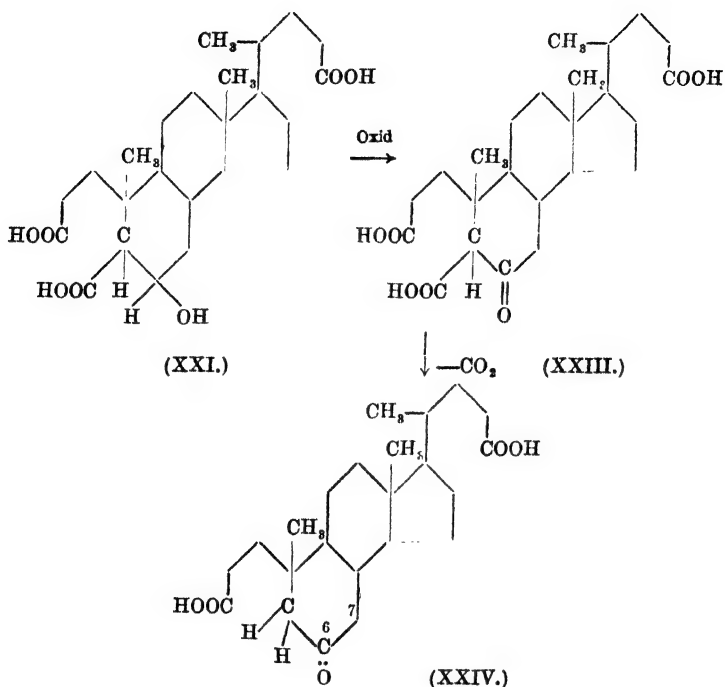
↓ Reduction

(XXII.)

Hydroxylithobilianic acid (XXI.), on mild oxidation, yields ketolithobilianic acid (XXIII.), which is unstable and passes into the *allo*-stereoisomer. *Allo*ketolithobilianic acid (XXIII.) is a β-ketonic acid, since it readily splits off carbon dioxide, yielding the keto-dicarboxylic acid (XXIV.). From these

results it follows that hyodeoxycholic acid is 3 : 6-dihydroxycholanic acid.[1] The formulæ given will make the changes clearer,

(XXI.) Oxid → (XXIII.)

↓ $-CO_2$

(XXIV.)

Chenodeoxycholic acid (XXV.), on oxidation, yields chenodeoxybilianic acid (XXVI.).[2] Further oxidation produces chenocholoidanic acid (XXVII.), which is a malonic acid, and on heating gives a tetrabasic acid (XXVIII.).[3] This tetrabasic acid is also formed by the oxidation of the ketodicarboxylic acid (XXIV.) derived from hyodeoxycholic acid. It is therefore concluded that chenodeoxycholic acid has an hydroxyl group attached to a carbon atom adjacent to carbon atom 6 in the same ring, *i.e.*, at carbon atom 7.

Chenodeoxycholic acid is therefore 3 : 7 dihydroxycholanic acid.

[1] Windaus, Grimmel and von Staden, *Z. physiol. Chem.*, 1921, **117**, 146; Windaus, *Annalen*, 1926, **447**, 233.

[2] Windaus and van Schoor, *Z. physiol. Chem.*, 1926, **157**, 177.

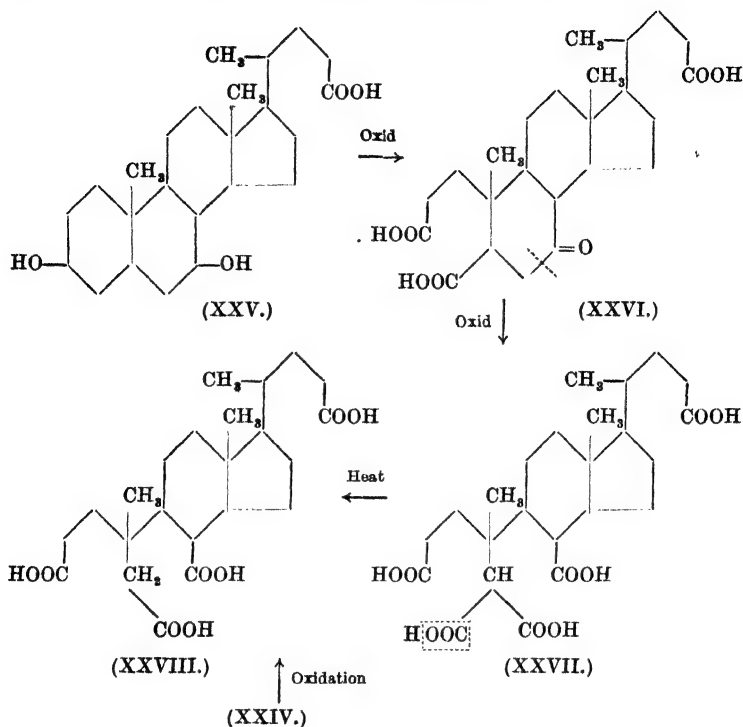
[3] Wieland and Jacobi, *ibid.*, 1925, **148**, 232.

(XXV.) —Oxid→ (XXVI.)

Oxid ↓

(XXVIII.) ←Heat— (XXVII.)

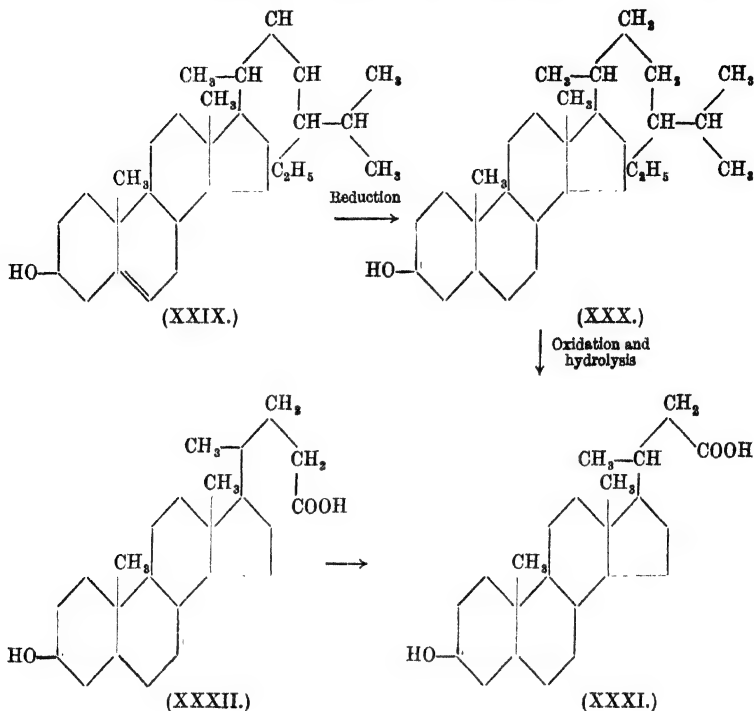
↑ Oxidation

(XXIV.)

The position of the hydroxyl group in ergosterol and in stigmasterol has been shown to be the same as in cholesterol.[1] The three sterols can be reduced to the corresponding saturated alcohols, cholestanol, ergostanol and stigmastanol (XXX.). The acetates of ergostanol and stigmastanol on oxidation by chromic acid followed by hydrolysis yield β-3-hydroxy*allo*-*nor*cholanic acid (XXXI.). Cholestanol acetate yields β-3-hydroxy*allo*cholanic acid (XXXII.) which on shortening the side-chain by the successive actions of phenyl magnesium bromide and chromic acid also gives rise to β-3-hydroxy*allonor*cholanic acid. This evidence establishes the fact that all three sterols have the hydroxyl group in the same position in the ring system and in the same stereochemical arrangement. The steps in the formation of β-3-hydroxy*allonor*cholanic acid are illustrated by reference to stigmasterol (XXIX.).

[1] Fernholz and Chakravorty, *Ber.*, 1934, 67, [B], 2021.

(XXIX.) —Reduction→ (XXX.)

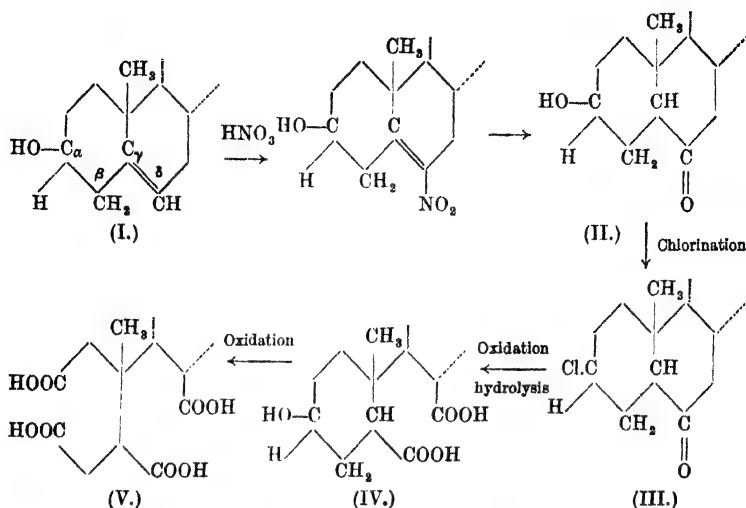
(XXX.) —Oxidation and hydrolysis→ (XXXI.)

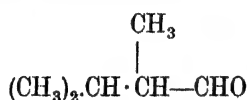
(XXXII.) → (XXXI.)

E.—The Double Bonds of the Sterols

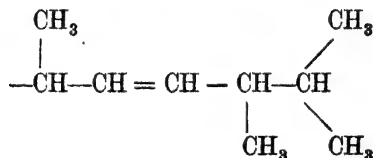
It has been established that cholesterol is an unsaturated alcohol in which the hydroxyl group and the double bond are in α–$\gamma\delta$ positions relative to each other, and in different rings. The various decompositions of cholesterol are readily explained on this basis. When cholesterol (acetate) (I.) is nitrated and then oxidized, cholestanonol (II.) is formed. This keto alcohol is converted into the chloroketone (III.), oxidized and hydrolysed, giving rise to a dibasic hydroxy acid (IV.), which on further oxidation yields a tetrabasic acid (V.) without loss of carbon atoms from the molecule. The tetrabasic acid is not a malonic acid derivative. These changes can only be explained on the assumption that the hydroxyl group and the double bond are in separate rings. These steps may be outlined as follows:

CH_3 HO—C_α C_γ β δ H CH_2 CH (I.) $\xrightarrow{HNO_3}$ CH_3 HO—C C H CH_2 NO_2 ⟶ CH_3 HO—C CH H CH_2 C=O (II.)

↓ Chlorination

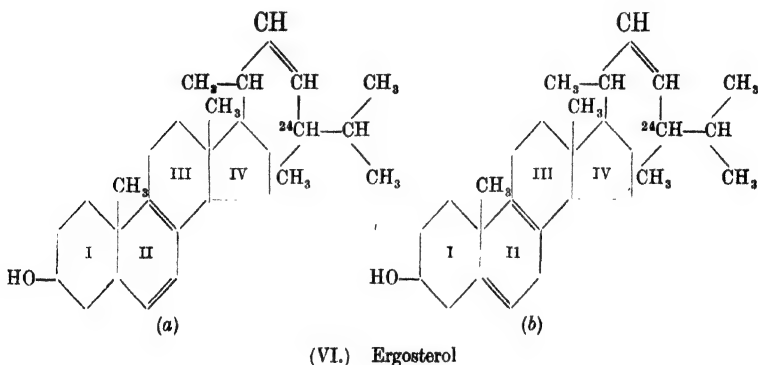
CH_3 Cl.C CH H CH_2 C=O (III.) $\xrightarrow[\text{hydrolysis}]{\text{Oxidation}}$ CH_3 HO—C CH COOH H CH_2 COOH (IV.) $\xrightarrow{\text{Oxidation}}$ CH_3 HOOC HOOC COOH COOH (V.)

Compared with cholesterol, ergosterol contains an extra methyl group and has three double bonds in the molecule, one of which is in the side-chain. The action of ozone on ergosterol yields methyl isopropyl acetaldehyde,

$$(CH_3)_2.CH\cdot\underset{}{\overset{CH_3}{\overset{|}{C}H}}—CHO$$

as one of the products.[1] This leads to the conclusion that the structure of the ergosterol side-chain is

$$—\overset{CH_3}{\overset{|}{C}H}—CH=CH—\underset{CH_3}{\underset{|}{C}H}—CH\begin{matrix}CH_3\\CH_3\end{matrix}$$

Only two of the double bonds of ergosterol are capable of adding on hydrogen directly under catalytic influence. The first double bond to be attacked is in the nucleus, since the action of ozone yields methyl isopropyl acetaldehyde from the dihydro-compound. Further action of hydrogen leads to the side-chain double bond being saturated as the tetrahydro-derivative,

[1] Reindel and Kipphan, *Annalen*, 1932, **493**, 181; Windaus, von Werder and Gschaider, *Ber.*, 1932, **65**, [B], 1006.

α-ergostenol, does not yield the aldehyde on ozonization. The third double bond completely resists direct hydrogenation. These results point to the inert double bond being situated between two quaternary carbon atoms. The other nuclear double bond is said to be conjugated with the inert linkage, as ergosterol combines with maleic anhydride.[1] It is inferred that the nuclear double bonds are in the same ring on account of the ready production of a methyl benzene tetracarboxylic acid from ergosterol. Inspection of the formula (*a*) shows that ring II. fulfils these conditions. On the other hand, from a study of certain triol derivatives of ergosterol, cogent reasons have been given for placing the reactive nuclear double bond at position C_5–C_6, as in formula VI. (*b*).[2]

(*a*) (*b*)

(VI.) Ergosterol

This is fully supported by the fact that ergosterol (VI.) on oxidation, hydrolysis and hydrogenation was converted into a saturated triol (VII.), which yielded the ergostanoldione (VIII.) on oxidation. This substance on dehydration was converted into the ergostenedione (IX.). The unsaturated diketone was reduced to the saturated ketone (X.), which was converted into a cyclic azine (XI.) by the action of hydrazine.[3] This final formation proves the dione (X.) to be a γ-compound, and points to the presence of an ethylenic linkage at the 5–6 position in ergosterol. If the evidence of conjugation is considered beyond

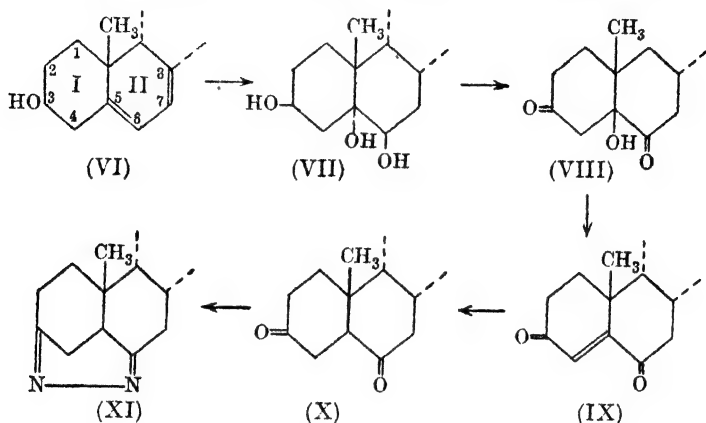
[1] Windaus and Lüttringhaus, *Ber.*, 1931, **64**, [B], 850; Windaus and Langer, *Annalen*, 1933, **508**, 105.

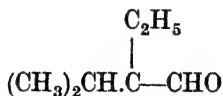
[2] Dunn, Heilbron, Phipers, Samant and Spring, *J.*, 1934, 1576.

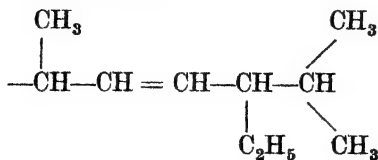
[3] Windaus, Inhoffen, and Reichel, *Annalen*, 1934, **510**, 248.

dispute then the second nuclear ethylenic linkage must be placed between carbon atoms 7 and 8 of ring II. (VI *b*.). It will be noted that the changes outlined above are parallel, step by step, with those which took place when stigmasterol was treated in the same way (see page 29). Similarly cholesterol yielded comparable substances and an azine, so that all three sterols have an ethylenic linkage between carbon atoms 5 and 6 of ring II.

(VI) → (VII) → (VIII)

(XI) ← (X) ← (IX)

Stigmasterol contains one carbon atom more than ergosterol and has two double bonds in the molecule. The extra carbon atom is in the side-chain, a C_2H_5 group taking the place of the methyl group at C_{24}. One of the two double bonds of stigmasterol is in the side-chain, as ozonization yields ethyl *iso*propylacetaldehyde : [1]

$$(CH_3)_2CH.\underset{}{\overset{C_2H_5}{\overset{|}{C}}}—CHO$$

The structure of the side-chain is therefore,

$$—\overset{CH_3}{\overset{|}{C}H}—CH = CH—\underset{C_2H_5}{\underset{|}{C}H}—CH\begin{matrix}CH_3\\CH_3\end{matrix}$$

[1] Guiteras, *Z. physiol. Chem.*, 1933, **214**, 89.

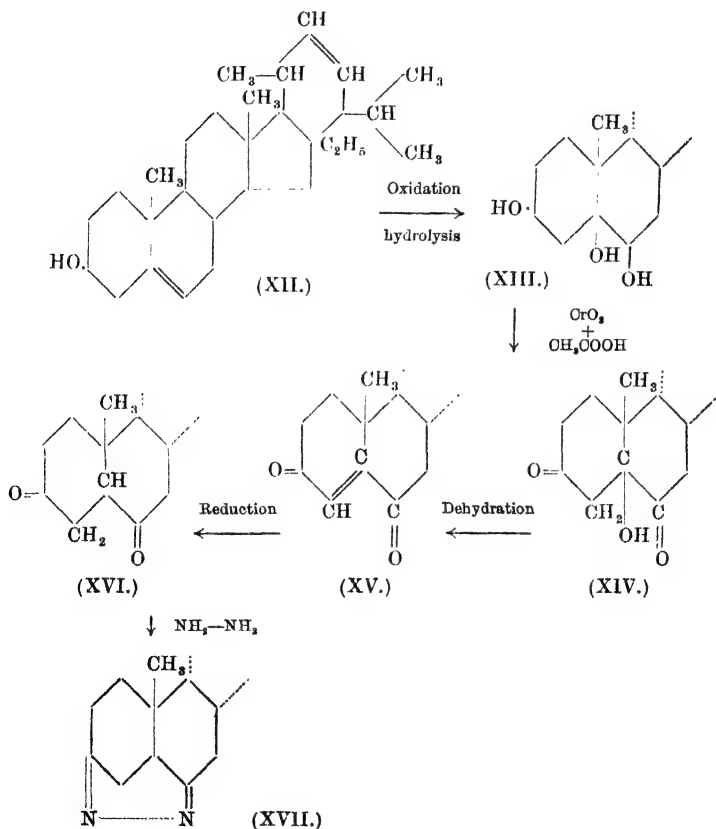
It is concluded that the nuclear double bond is in the position C_5–C_6 from the results obtained by the oxidation of stigmasterol (acetate) (XII.), followed by hydrolysis which yielded stigmastenetriol (XIII.). The triol contains a tertiary hydroxyl group, as chromic acid-acetic acid oxidation gives rise to stigmastenoldione (XIV.). Dehydration of this compound produces stigmastadienedione (XV.) and reduction of this yields stigmastenedione (XVI.). Stigmastenedione when acted upon by hydrazine yields an azine (XVII.). This formation of a cyclic azine shows the dione to be a γ-compound,[1] as follows :

(XII.) —Oxidation, hydrolysis→ (XIII.)

↓ CrO_3 + CH_3COOH

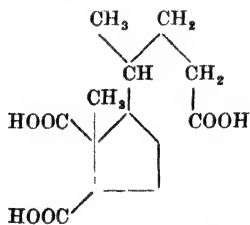
(XIV.) —Dehydration→ (XV.) —Reduction→ (XVI.)

↓ NH_2—NH_2

(XVII.)

[1] Wieland, Schlichting, and Jacobi, *Z. physiol. Chem.*, 1934, **508**, 215.

F.—The Stereochemistry of the Bile Acids and Sterols

The cholane compounds have a flat molecule. This is demanded by X-ray measurements.[1] With angular fusion of the rings, as in the cholane skeleton, this flatness is only possible if rings II. and III. are connected in a *trans*-position. Rings I. and II. can be connected in two ways, and both types of compound are well known. The available experimental evidence indicates that rings I. and II. in cholestane and its derivatives are *trans*-compounds, whilst coprostane and its derivatives are the *cis*-isomers. These conclusions are supported by the results of comparisons of the densities, melting points and refractive indices of cholestane and corpostane with those of *trans*- and *cis*-decalins.[2] The difference between cholestane and coprostane is therefore due to the spatial orientation of the hydrogen atom at C_5. It is also concluded that rings III. and IV. are fused in a *trans*-position, as the acid,

CH_3 CH_2
CH CH_2
CH_3
HOOC COOH
HOOC

obtained from different bile acids is a *trans*-acid.[3]

The configuration of cholestane will be, on these assumptions, *trans-trans-trans*, and coprostane, *cis-trans-trans.*

Much systematic work has yet to be done on the stereochemistry of these compounds. In conclusion, attention may be drawn to the interesting speculation [4] on the syntheses of cholesterol and the bile acids by animal organisms. The derivation of the complex cholane grouping is possible from three hexose units and should not be beyond the powers of the animal organism, and, in fact, ergosterol can be built up from a medium containing a hexose and mineral salt only, by yeast and moulds.

[1] Bernal, *Nature*, 1932, **129**, 277; *Chem. and Ind.*, 1932, **51**, 259. 466; Ruzicka and Thomann, *Helv. Chim. Acta*, 1933, **16**, 216.

[2] Ruzicka, Furter, and Thomann, *Helv. Chim. Acta*, 1933, **16**, 327.

[3] Wieland and Dane, *Z. physiol. Chem.*, 216, **91**, (1933).

[4] Rosenheim and King, *Chem. and Ind.*, 1932, **51**, 464.

CHAPTER II

VITAMINS

A.—Introductory

There are two main factors which influence the growth of animal tissues, one is the capacity of the cell to grow—the growth factor; the other is the availability of material on which the tissues may grow—the food factor. Very little is known of the growth factor. On the other hand, our knowledge of the relation of food to growth is extensive and constantly increasing. The materials out of which living tissues are built up are oxygen, water, inorganic salts, carbohydrates, fats and proteins. With increase of knowledge of nutrition it became apparent that other substances were essential for growth and for the maintenance of bodily equilibrium. These substances, necessary only in minute quantities, are the "accessory food factors" or "vitamins." When there is a deficiency of vitamins in the diet of young animals, growth is retarded, and in adults a deficiency leads to various diseases. It is known with certainty that rickets, beri-beri, scurvy and xerophthalmia are due to the absence of one or other of the vitamins.

With a few exceptions the vitamins are formed by plants. In some cases the plant produces a precursor, which in the animal body is converted into the active vitamin. Thus ergosterol on irradiation with ultra-violet light passes into calciferol (vitamin D_2), and the conversion of carotene into vitamin A takes place in the animal liver. Certain animals, however, appear to be able to synthesize *l*-ascorbic acid (vitamin C), as this substance appears in the livers of calves and chickens reared on diets free from the vitamin. From biological investigations a number of vitamins of, as yet, unknown chemical structure have been proved to exist. The vitamins which have been isolated and have had their constitutions established are/vitamin A; the vitamin B complex including vitamin B_1 (aneurin), *d*-riboflavin,

pantothenic acid, adermin and nicotinic acid; vitamin C (*l*-ascorbic acid); the vitamin D group including calciferol (vitamin D_2), and vitamin D_3; the vitamin E group (α-, β- and γ-tocopherols); and vitamins K_1 and K_2.

B.—Vitamin A

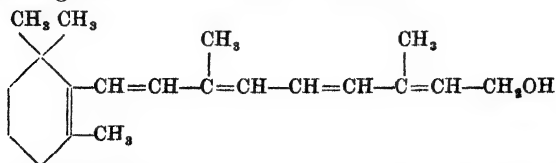
1. *Properties of Vitamin A*

In addition to influencing growth, there is evidence that an adequate supply of vitamin A increases the resistance of human beings to certain types of ill-health. Vitamin A occurs in fats and blood, and is found in relatively high concentrations in the livers of fish. It may be prepared in concentrated form by hydrolysing fat with alcoholic potash in an inert atmosphere to prevent oxidation. The vitamin remains in the unhydrolysed residue. Cholesterol may be removed by crystallization from methyl alcohol solution. Further purification is effected by fractional distillation in vacuo.

2. *Constitution of Vitamin A*

The vitamin has been isolated as a viscous yellow oil.[1] The molecular formula $C_{20}H_{30}O$ has been assigned to it, though molecular weight determinations in camphor by Rast's method resulted in a value of 320 being obtained. The vitamin yields uncrystallizable esters with *p*-nitrobenzoic and acetic acids, and oxidation of it with ozone yields geronic acid, in amount indicating the presence of one ionone residue in the molecule.[2] With potassium permanganate as the oxidizing agent, acetic acid is obtained. On treatment with hydrochloric acid and alcohol the vitamin is converted into a cyclic compound, and this, on dehydrogenation with selenium, yields 1 : 6-dimethyl naphthalene.[3]

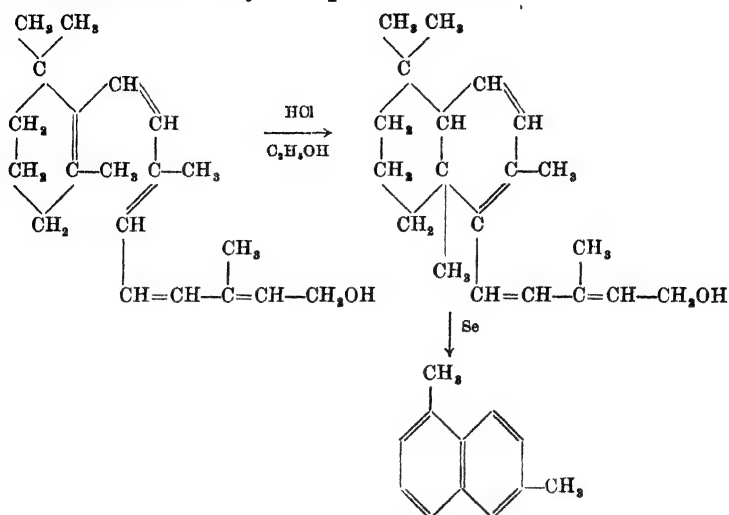
Assuming the structure of vitamin A to be,

CH_3 CH_3 (gem-dimethyl on ring) ; ring —CH=CH—C(CH_3)=CH—CH=CH—C(CH_3)=CH—CH_2OH ; ring —CH_3

[1] Karrer, Morf, and Schopp, *Helv. Chim. Acta*, 1931, **14**, 1036, 1431; Heilbron et al., *Biochem. J.*, 1932, **26**, 1178.

[2] Karrer, *Nature*, 1931, **128**, 842.

[3] Heilbron, Morton and Webster, *Biochem. J.*, 1932, **26**, 1194.

these conversions may be explained as follows :

```
CH3 CH3                                    CH3 CH3
  \ /                                        \ /
   C                                          C
  / \   /CH\                                 / \   /CH\
CH2  ||     CH        HCl               CH2  CH    CH
 |   ||     |     ---------->            |    |     |
CH2  C—CH3  C—CH3   C2H5OH              CH2   C     C—CH3
  \ /      //                             \ /|\   //
  CH2     CH                              CH2 |  C
          |       CH3                         |  |       CH3
          |       |                        CH3|  |       |
          CH=CH—C=CH—CH2OH                       CH=CH—C=CH—CH2OH
                                              | Se
                                              v
                                             CH3
                                              |
                                           (naphthalene ring)—CH3
```

Vitamin A can be reduced by aluminium amalgam, taking up five molecules of hydrogen to yield a fully saturated alcohol. This reduced vitamin A, named perhydrovitamin A, has been synthesized from β-ionone by the following steps : β-ionone (I.) and bromoethylacetate, when condensed in hot benzene solution by means of zinc, give ethyl δ-2 : 6 : 6-trimethyl-Δ′-cyclohexenyl-β-methyl-$\Delta^{\alpha\gamma}$-butadiene-α-carboxylate (II.). This ester is reduced by means of hydrogen, using platinum as a catalyst, to the fully saturated ester (III.). The ester is further reduced by sodium and ethyl alcohol to the corresponding amyl alcohol derivative (IV.). The bromide (V.) of this alcohol is converted by the malonic ester synthesis into the heptoic acid derivative (VII.), the acid chloride (VIII.) of which reacts with zinc methyl iodide to yield a ketone (IX.). Zinc and bromoethylacetate react with the ketone, yielding ethyl β-hydroxy-θ-2 : 6 : 6 trimethyl*cyclo*hexyl-βγ-dimethylnonoate (X.). When the hydroxyl group of this compound is replaced by a hydrogen atom *via* the bromide (XI.), and then reduced with sodium and ethyl alcohol, an alcohol (XIII.) is formed which is identical with perhydrovitamin A, obtained by the reduction of vitamin A from natural sources. The following outline will make the steps in the synthesis clearer :

(I.) $\xrightarrow[Zn]{Br.CH_2.COOEt}$ (II.) $\xrightarrow{H_2}$ (III.) $\xrightarrow[EtOH]{Na}$ (IV.) $\xrightarrow{\text{Bromination}}$ (V.) $\xrightarrow{Na.CH(COOEt)_2}$ (VI.) $\xrightarrow{-CO_2 \text{ and hydrolysis}}$ (VII.) $\xrightarrow{\text{Chlorination}}$ (VIII.) $\xrightarrow{ZnCH_3I}$ (IX.) $\xrightarrow[Zn]{Br.CH_2COOEt}$ (X.) $\rightarrow$ (XI.) $\rightarrow$ (XII.) $\xrightarrow{\text{Reduce}}$ (XIII.)

(I.) $(CH_3)_2C$ ring: H_2C, H_2C, CH_2; $C—CH{=}CH—CO(CH_3)$; $C—CH_3$

(II.) ring $—CH{=}CH—C(CH_3){=}CH.COOEt$, $—CH_3$

(III.) ring (H) $—CH_2—CH_2—CH(CH_3)—CH_2.COOEt$, $—CH_3$

(IV.) ring $—CH_2—CH_2.CH(CH_3).CH_2.CH_2OH$, $—CH_3$

(V.) ring $—(CH_2)_2.CH(CH_3).(CH_2)_2Br$, $—CH_3$

(VI.) ring $—(CH_2)_2—CH(CH_3).(CH_2)_2CH(COOEt)_2$, $—CH_3$

(VII.) ring $—(CH_2)_2—CH(CH_3).(CH_2)_3.COOH$, $—CH_3$

(VIII.) ring $—(CH_2)_2—CH(CH_3).(CH_2)_3COCl$, $—CH_3$

(IX.) ring $—(CH_2)_2.CH(CH_3)—(CH_2)_3—CO(CH_3)$, $—CH_3$

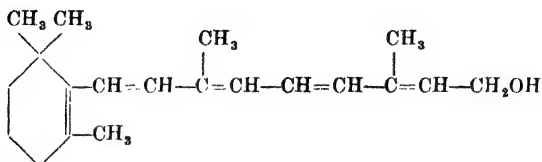
(X.) ring $—(CH_2)_2.CH(CH_3)—(CH_2)_3—C(CH_3)(OH)—CH_2.COOEt$, $—CH_3$

(XI.) ring $—(CH_2)_2—CH(CH_3)—(CH_2)_3—C(CH_3)(Br)—CH_2.COOEt$, $—CH_3$

(XII.) ring $—(CH_2)_2—CH(CH_3).(CH_2)_3.CH(CH_3).CH_2COOEt$, $—CH_3$

(XIII.) $(CH_3)_2C$ ring: H_2C, H_2C, CH_2; $C(H)—(CH_2)_2.CH(CH_3).(CH_2)_3.CH(CH_3).CH_2.CH_2OH$; $C(H)—CH_3$

In spite of the fact that vitamin A has not been isolated in a crystalline condition, the evidence is strongly in favour of the structure

$$\begin{array}{l} CH_3\ CH_3 \qquad\qquad\qquad CH_3 \qquad\qquad\qquad CH_3 \\ \qquad\qquad\qquad\qquad\quad | \qquad\qquad\qquad\qquad\quad | \\ \text{(ring)}\!-\!CH{=}CH{-}C{=}CH{-}CH{=}CH{-}C{=}CH{-}CH_2OH \\ \qquad\quad -CH_3 \end{array}$$

Extensive spectrographic examinations of vitamin A concentrates from different sources indicate the presence of very little impurity (if any) in the oils isolated.[1]

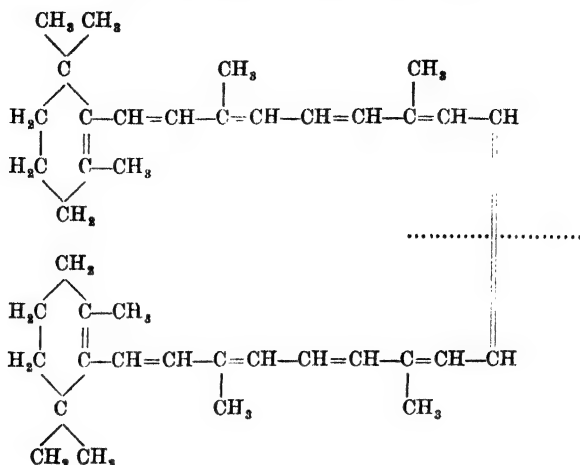
3. *Vitamin A and the Carotenes*

The relationship of vitamin A to the carotenes is a very close one, and valuable information on the vitamin structure has been obtained by the chemical study of these pigments. At the present time the opinion is held that the growth-promoting effects associated with green vegetables are due to the carotenes present, and not to vitamin A, as was formerly thought.

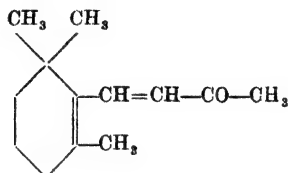
There are three carotenes occurring together in varying amounts in a great variety of plants. They are distinguished as α-, β- and γ-carotene.[2] The γ-carotene, which is present in crude carotene in small amounts, may be separated from the other two by adsorption on aluminium oxide. The β-form, which makes up the major portion of crude carotene, may be isolated from the α-compound by adsorption from ligroin solution on calcium hydroxide or oxide. The connection with vitamin A gave an impetus to research on these pigments, and in a very short time remarkable progress was made in the elucidation of the molecular structures of the carotenes and other naturally occurring polyene compounds. The three carotenes are isomeric, and have been given the molecular formula $C_{40}H_{56}$. Interest has mainly centred round β-carotene, and the symmetrical structure,

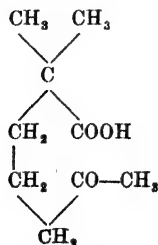
[1] Heilbron, Morton, Drummond et al., *Biochem. J.*, 1932, **26**, 1178.

[2] Kuhn and Lederer, *Naturwissenschaften*, 1931, **19**, 306; Karrer et al., *Helv. Chim. Acta*, 1931, **14**, 614; Rosenheim and Starling, *Chem. and Ind.*, 1931, **50**, 443.

```
      CH3 CH3
        \/
        C               CH3                CH3
       / \              |                  |
   H2C    C—CH=CH—C=CH—CH=CH—C=CH—CH
    |     ||                                         :
   H2C    C—CH3                                      :
       \ /                                           :
       CH2                                           :
                                         ............|............
       CH2                                           |
       / \                                           |
   H2C    C—CH3                                      ||
    |     ||                                         ||
   H2C    C—CH=CH—C=CH—CH=CH—C=CH—CH
       \ /              |                  |
        C               CH3                CH3
       / \
     CH3 CH3
```

was attributed to it.

On catalytic hydrogenation eleven molecules of hydrogen are absorbed, the last stage of reduction yields a hydrocarbon $C_{40}H_{78}$, indicating that the molecule is in part dicyclic. The action of cold permanganate solution produces ionone,

```
      CH3   CH3
        \   /
         \ /
         / \
        /   \—CH=CH—CO—CH3
       |    ||
       |    ||—CH3
        \   /
         \ /
```

and the detection of geronic acid,

```
      CH3  CH3
        \  /
         C
        / \
      CH2  COOH
      |
      CH2  CO—CH3
        \  /
         CH2
```

amongst the products of oxidation by ozone confirms the presence of the ionone skeleton in the β-carotene molecule. Six molecular

proportions of acetic acid are obtained from one of carotene by oxidation with chromic acid, and when the oxidizing agent used is potassium permanganate four molecular proportions of acetic acid (presumably from four $—C(CH_3)=$ groupings) and some α-α-dimethyl glutaric acid are produced. Thermal degradation of β-carotene yields toluene, *m*-xylene and 2 : 6-dimethyl naphthalene. The production of 2 : 6-dimethyl naphthalene may be explained by assuming that cyclization takes place in the side-chain and that the ionone ring is not involved, as in the case of the formation of 1 : 6-dimethylnaphthalene from vitamin A.

β-carotene in benzene solution, on careful oxidation with chromic acid, yields semi-β-carotenone (I.), and on further oxidation β-carotenone (II.) is obtained.[1] These two compounds may be represented as :

[1] Kuhn and Winterstein, *Ber.*, 1933, **66**, [B], 429.

```
                        CH3  CH3                   CH3  CH3                     CH3  CH3
 CH3  CH3                  \ /                        \ /                          \ /
    \ /                     C                          C                            C
     X                     / \                        / \                          / \
    / \—(C22H26)—C          CH2         and      H2C      C—(C22H26)—C               CH2
   |   ||        ¨O          |                    |       ¨O         ¨O               |
   |   ||—CH3                |                    |                                   |
   |   |         O           |                    |       O          O                |
    \ /     CH3—¨C          CH2                  H2C      ¨C—CH3  CH3—¨C             CH2
                   \        /                       \      /              \          /
                      CH2                              CH2                    CH2
            (I.)                                                   (II.)
```

Semi-β-carotenone exhibits strong growth-promoting properties when tested on rats, and this is attributed to the presence of one β-ionone skeleton in the molecule. β-carotenone shows no growth-promoting properties when tested in the same way. It has been shown that β-carotene is the precursor of vitamin A in the animal body, one molecule of the carotene giving rise to two molecules of the vitamin. Large quantities of carotene fed to rats led to the storage of vitamin A in the liver.[1] The presence of vitamin A in the liver was not due to traces of it in the original carotene as absorption spectra results clearly proved.[2]

C.—The Vitamin B Complex

1. *Introductory*

This growth-promoting complex is widely distributed in foodstuffs. The richest sources are rice polishings, wheat germ and yeast. Vitamin B was at first thought to be a single substance and was called the water-soluble B factor. It is now known to contain a thermolabile compound (vitamin B_1 or aneurin) and a thermostable part, of which vitamin B_2 (riboflavin), pantothenic acid, vitamin B_6 (adermin), nicotinic acid and the biotins are components of known structure. This thermostable part is frequently referred to as the vitamin B_2 complex. The compounds of the vitamin B complex vary considerably in structure. The diagram (I.) contains the structural formulae of the more interesting compounds of the complex so far examined.

[1] Moore, *Biochem. J.*, 1929, **23**, 803, 1267.
[2] Capper, *ibid.*, 1930, **24**, 453, 980.

Vitamin B Complex
Thermolabile
Thermostable
Vitamin B1 (aneurin, thiamin)
(antineuritic factor)
Vitamin B2 Complex
d-Riboflavin
(growth promoting)
Pantothenic acid
(chick dermatitis factor)
Adermin
(rat antidermatitis factor)
Nicotinic acid
(human antipellagra factor)
The Biotins

2. *Vitamin* B_1

(*a*) *General.*—This vitamin has been isolated in the form of crystalline salts by different methods.[1] The chloride hydro-chloride has been fully examined and the formula

$$C_{12}H_{17}ON_4ClS.HCl$$

given to it.

(*b*) *The Degradation Products.*—Oxidation of the vitamin hydrochloride with nitric acid splits it into two acidic substances, $C_5H_6O_2N_2$ (*a*) and $C_5H_5O_2NS$ (*b*).[2] At ordinary temperature the vitamin yields a base, C_6H_9ONS (*c*) and an acid $C_6H_9O_3N_3S$ (*d*) when treated with sodium sulphite solution saturated with sulphur dioxide. This unusual reagent was employed as it had previously been found that the vitamin concentrate from rice lost its antineuritic activity after contact with sulphurous acid.[3] The base (*c*) on oxidation with nitric acid yields the acid (*b*) which was also obtained directly from the vitamin by nitric acid oxidation. When the vitamin is oxidized with barium permanganate a base $C_6H_{10}N_4$ (*e*) is obtained.[4] These decomposition products have been fully examined and the structures of four out of five mentioned above confirmed by their syntheses. The acid $C_5H_5O_2NS$ (*b*) was identified as 4-methylthiazole-5-carboxylic acid (IX.) [5] and the base, C_6H_9ONS (*c*) was proved by its synthesis to be 4-methyl-5-β-hydroxyethylthiazole (VIII.).

In this synthesis, ethyl acetoacetate (I.) and ethyl-β-bromoethyl ether (II.) were condensed by means of sodium in absolute alcoholic solution to yield ethyl α-2-ethoxyethylacetoacetate (III.). Treatment of the ester with sulphuryl chloride gave ethyl α-chloro-α-2-ethoxyethylacetoacetate (IV.). The ester grouping was eliminated giving rise to methyl α-chloro-γ-ethoxypropyl ketone (V.). Condensation of the ketone with thioformamide yielded 4-methyl-5-β-ethoxyethylthiazole (VI.) The ethoxyl group was replaced by chlorine (VII.) and the chlorine atom in its turn was eliminated by the action of hot water giving

[1] Jansen and Donath, *Proc. K. Akad. Wetensch. Amsterdam*, 1926, **29**, 1390; **35**, 293; Windaus et al., *Z. physiol. Chem.*, 1932, **204**, 123; Otake, *J. Agric. Chem. Soc. Japan*, 1931, **7**, 775; Williams, Waterman, and Keresztesy, *J. Amer. Chem. Soc.*, 1934, **56**, 1187; 1935, **57**, 517, 536, 1093, 1751.

[2] Windaus, Tschesche, and Grewe, *Z. physiol. Chem.*, 1934, **228**, 27.

[3] Williams, *J. Amer. Chem. Soc.*, 1935, **57**, 229.

[4] Windaus, Tschesche and Grewe, *Z. physiol. Chem.*, 1935, **237**, 98.

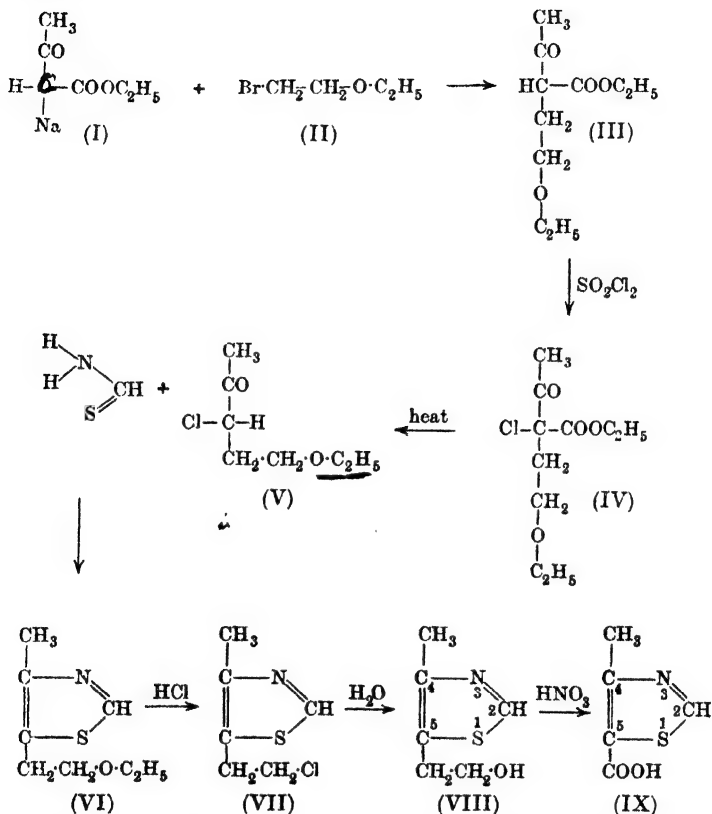
[5] Wohmann, *Annalen*, 1890, **259**, 299; Tomlinson, *J.*, 1935, 1030.

rise to 4-methyl-5-β-hydroxyethylthiazole (VIII.) identical with the compound obtained from the vitamin.[1] The structural steps are,

$$\underset{\text{(I)}}{CH_3\cdot CO\cdot C(Na)H\text{—}COOC_2H_5} + \underset{\text{(II)}}{Br\cdot CH_2\cdot CH_2\cdot O\cdot C_2H_5} \longrightarrow \underset{\text{(III)}}{CH_3\cdot CO\cdot HC(CH_2\cdot CH_2\cdot O\cdot C_2H_5)\text{—}COOC_2H_5}$$

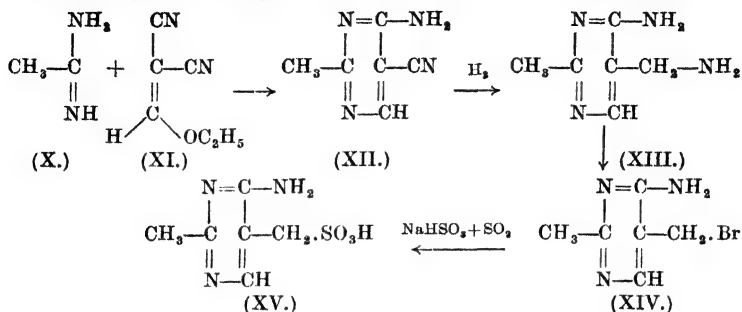
$$\text{(III)} \xrightarrow{SO_2Cl_2} \underset{\text{(IV)}}{CH_3\cdot CO\cdot Cl\text{—}C(CH_2\cdot CH_2\cdot O\cdot C_2H_5)\text{—}COOC_2H_5} \xrightarrow{\text{heat}} \underset{\text{(V)}}{CH_3\cdot CO\cdot Cl\text{—}CH\cdot CH_2\cdot CH_2\cdot O\cdot C_2H_5}$$

$$H_2N\cdot CH{=}S + \text{(V)} \longrightarrow \text{(VI)}$$

$$\underset{\text{(VI)}}{\text{4-}CH_3\text{, 5-}CH_2\cdot CH_2\cdot O\cdot C_2H_5\text{-thiazole}} \xrightarrow{HCl} \underset{\text{(VII)}}{\text{4-}CH_3\text{, 5-}CH_2\cdot CH_2\cdot Cl\text{-thiazole}} \xrightarrow{H_2O} \underset{\text{(VIII)}}{\text{4-}CH_3\text{, 5-}CH_2\cdot CH_2\cdot OH\text{-thiazole}} \xrightarrow{HNO_3} \underset{\text{(IX)}}{\text{4-}CH_3\text{, 5-}COOH\text{-thiazole}}$$

From its properties the acid product $C_6H_9O_3N_3S$ (*d*) was thought to be a pyrimidine derivative. Its synthesis showed this assumption to be correct, and the compound to be 6-amino-2-methylpyrimidine-5-methylsulphonic acid (XV.). The steps in the synthesis are as follows. Acetamidine (X.) and ethoxymethylenemalondinitrile (XI.) were condensed in alcoholic solution to yield 6-amino-5-cyano-2-methylpyrimidine (XII.). The cyano-derivative in acetic acid was treated with gaseous hydrogen chloride and then catalytically reduced to 6-amino-2-methyl-5-aminomethylpyrimidine (XIII.), which proved to be

[1] Clarke and Gurin, *J. Amer. Chem. Soc.*, 1935, 57, 1876.

the same as the base (*e*) obtained from the vitamin by permanganate oxidation. This compound was converted into the corresponding 5-bromomethyl-derivative (XIV.), which in aqueous solution was treated with sodium hydrogen sulphite and sulphur dioxide to give the sulphonic acid (XV.).[1] The structures are :

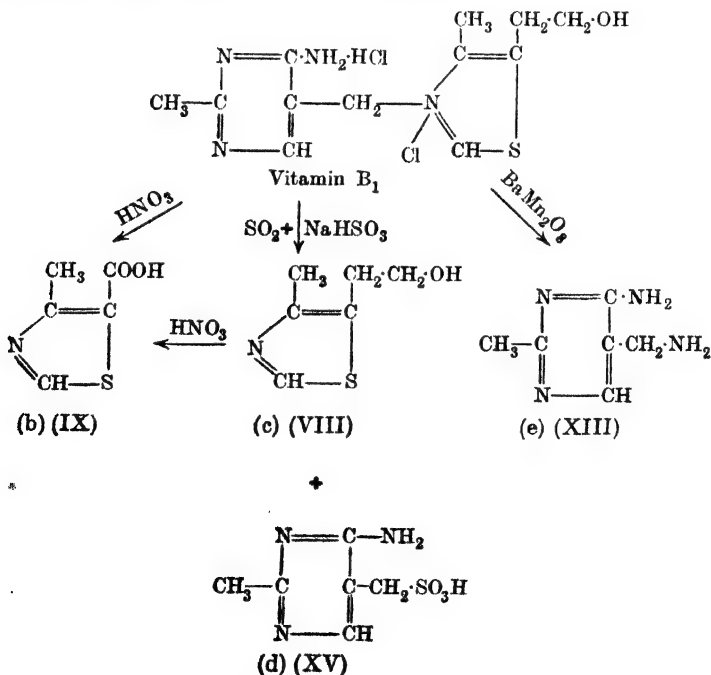
```
     NH2     CN                  N=C—NH2                    N=C—NH2
      |      |                   |  |                       |  |
CH3—C   +   C—CN       CH3—C   C—CN    H2    CH3—C   C—CH2—NH2
     ||      ||      —→          ||  ||     —→              ||  ||
     NH   H/ C \OC2H5            N—CH                       N—CH
                                                              |
   (X.)      (XI.)               (XII.)                       ↓ (XIII.)
              N=C—NH2                                   N=C—NH2
              |  |                                      |  |
      CH3—C   C—CH2.SO3H     NaHSO3+SO2       CH3—C   C—CH2.Br
              ||  ||          ←————                     ||  ||
              N—CH                                      N—CH
              (XV.)                                     (XIV.)
```

The diagram shows the structures of vitamin B_1 and its more important decomposition products.

```
                                          CH3   CH2·CH2·OH
                                          |     |
           N═══C·NH2·HCl                  C═══C
           |    |                        /     |
    CH3—C      C——CH2——N                      |
           ||   ||                     / \\    |
           N———CH                     Cl   CH—S
                 Vitamin B1

      HNO3 ↙        SO2+ ↓ NaHSO3          ↘ BaMnO4

  CH3  COOH            CH3  CH2·CH2·OH           N═══C·NH2
  |    |               |    |                    |    |
  C═══C      HNO3      C═══C            CH3—C      C·CH2·NH2
 /     |     ←——      /     |                   ||    ||
N      |             N      |                   N———CH
 \\    |              \\    |
  CH——S                CH——S
 (b) (IX)              (c) (VIII)                (e) (XIII)

                          +

                N═══C—NH2
                |    |
         CH3—C      C—CH2·SO3H
                ||   ||
                N———CH
                (d) (XV)
```

[1] Grewe, *Z. physiol. Chem.*, 1936, **242**, 89.

(c) *The Structure and Synthesis of Vitamin B_1.*—The identification of the thiazole and pyrimidine parts of the vitamin and the study of their properties finally permitted an adequate structure to be suggested for the compound.[1] This constitution was shortly afterwards confirmed by a synthesis which gave a product with the physiological, chemical and physical properties of vitamin B_1.[2] Other methods of synthesizing the vitamin have since been devised. The original method is given here. The interaction of sodium ethyl-β-ethoxypropionate (I.) and ethyl formate gave the formyl derivative (II.), which with acetamidine (III.) yielded 6-hydroxy-2-methyl-5-ethoxymethylpyrimidine (IV.). The hydroxyl group of the pyrimidine was displaced by chlorine by the action of phosphorus oxychloride. Alcoholic ammonia converted the chloride (V.) into the corresponding amine (VI.). The action of hydrobromic acid on the amine produced the bromide salt (VII.), which with 4-methyl 5-β-hydroxyethylthiazole (VIII.) yielded vitamin B_1 bromide hydrobromide (IX.). A methyl alcoholic solution of the hydrobromide was converted into the chloride hydrochloride (X.) by the action of silver chloride. Comparison of the physiological, chemical and physical properties of the synthetic and natural chloride hydrochlorides left no doubt about the identity of the two substances. The structural changes are :

[1] Williams, *J. Amer. Chem. Soc.*, 1936, **58**, 1063.
[2] Williams and Cline, *ibid.*, 1504 ; 1937, **59**, 1052.

(I) $C_2H_5O\cdot CO\cdot CH_2\cdot CH_2\cdot O\cdot C_2H_5$ —[$H\cdot COOC_2H_5$, Na]→ (II) $C_2H_5O\cdot CO\cdot CH(CH_2\cdot O\cdot C_2H_5)\cdot CHO$ → $CH_3\cdot C(=NH)\cdot NH_2$ + (III) $C_2H_5O\cdot CO\cdot CH(CH_2\cdot O\cdot C_2H_5)\cdot CHO$

↓ Condensation

(IV) 2-methyl-4-hydroxy-5-ethoxymethylpyrimidine: N=C–OH, CH_3–C, C–CH_2–O–C_2H_5, N—CH

—[$POCl_3$]→ (V) N=C–Cl, CH_3–C, C·CH_2·O·C_2H_5, N—CH

↓ NH_3

(VI) N=C–NH_2, CH_3–C, C·CH_2·O·C_2H_5, N—CH

—[HBr]→ (VII) N=C·NH_2·HBr, CH_3–C, C·CH_2·Br, N—CH

+

(VIII) thiazole: CH_3, CH_2·CH_2·OH, C=C, N, CH—S

→ (IX) N=C·NH_2·HBr, CH_3–C, C—CH_2—N(Br) (thiazolium: CH_3, CH_2·CH_2·OH, C=C, CH—S), N—CH

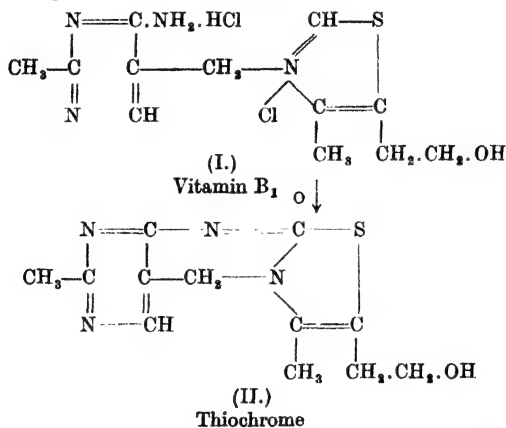
↓ AgCl

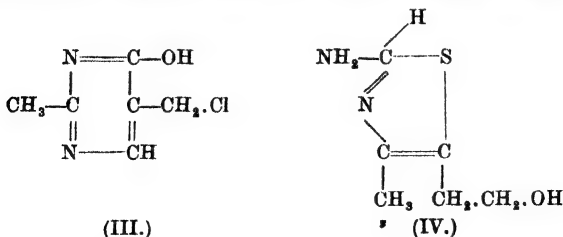
(X) N=C·NH_2·HCl, CH_3–C, C—CH_2—N(Cl) (thiazolium: CH_3, CH_2·CH_2·OH, C=C, CH—S), N—CH

(X) Vitamin B_1

(*d*) *Thiochrome.*—When an aqueous solution of vitamin B_1 was oxidized, the liquid showed a blue fluorescence.[1] Similarly solutions of the compound thiochrome obtained from yeast had a strong blue fluorescence. The molecular formula of thiochrome is $C_{12}H_{14}ON_4S$,[2] and that of vitamin B_1 $C_{12}H_{17}ON_4SCl.HCl$. This suggested that a close structural relationship might exist between the two compounds. This idea was confirmed when thiochrome was obtained from vitamin B_1 by alkaline potassium ferricyanide oxidation.[3] The structure assigned to thiochrome is (II.) and the change from vitamin B_1 (I.) may be represented as follows :—[4]

```
         N====C.NH2.HCl        CH——S
         |    |               //   |
   CH3—C    C———CH2———N      |
         ||   ||            / \    |
         N    CH          Cl   C===C
                               |   |
                  (I.)        CH3  CH2.CH2.OH
              Vitamin B1  O ↓

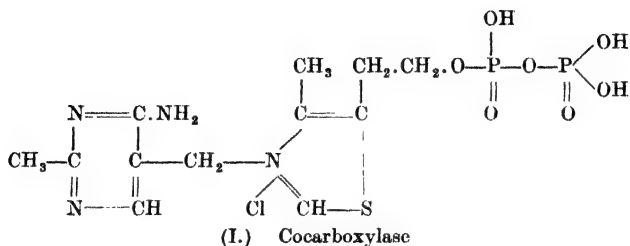
          N====C—— N——————C———S
          |    |         /    |
   CH3—C    C——CH2———N      |
          ||   ||         \   |
          N————CH          C===C
                           |   |
                          CH3  CH2.CH2.OH
                    (II.)
                 Thiochrome
```

This structure was confirmed by the synthesis of thiochrome, which was indistinguishable from the product obtained from the vitamin. The final stage of the synthesis was effected from the pyrimidine (III.) and thiazole (IV.) derivatives shown below.[5]

```
                                          H
                                         /
        N====C—OH               NH2—C————S
        |    |                      //    |
   CH3—C    C—CH2.Cl               N      |
        ||   ||                     \     |
        N————CH                      C===C
                                     |   |
                                    CH3  CH2.CH2.OH
          (III.)                        (IV.)
```

[1] Peters, *Nature*, 1935, **135**, 107.
[2] Kuhn et al., *Z. physiol. Chem.*, 1935, **234**, 196.
[3] Barger, Bergel and Todd, *Nature*, 1935, **136**, 259.
[4] Todd and Bergel, *J.*, 1936, 1559.
[5] Todd et al., *J.*, 1936, 1601.

(*e*) *Cocarboxylase.*—Many active enzyme preparations may be separated into two or more parts. A colloidal thermolabile part is obtained, and a second part consists of a thermostable crystalloidal organic substance, the coenzyme. The coenzyme plays an important rôle in the enzyme action, and the two separate parts must be present for full enzyme activity.

Carboxylase, one of the constituents of zymase from yeast, catalyses the decarboxylation of a number of keto-acids. Co-carboxylase has been isolated and found to be the pyrophosphoric acid ester (I.) of vitamin B_1.[1] The preparation of the coenzyme from the vitamin has been accomplished both by enzyme action and by treatment with pyrosphosphate or phosphorus oxychloride.[2]

```
                                                OH
                                                |      ,OH
                              CH3  CH2.CH2.O—P—O—P<
                               |    |           ||    || `OH
        N===C.NH2              C===C            O     O
        |     |               /     :
 CH3—C       C——CH2——N        :
        ||    ||             /\      :
        N——CH              Cl  CH——S
```

(I.) Cocarboxylase

3. *Vitamin* B_2

(*a*) *General.*—Vitamin B_2 usually occurs along with B_1 in natural substances, though there may be quantitative differences. It is necessary in the diet to maintain growth and health. It is present in yeast, milk, meat and green vegetables. It has been isolated from milk whey, analysed and given the molecular formula $C_{17}H_{20}O_6N_4$. It is relatively stable to heat, and on this property is based one of the methods of freeing it from vitamin B_1. Vitamin B_2 is soluble in water and alcohol and is broken down by the action of light. There is a very close connection between the vitamin and the yellow water-soluble

[1] Lohmann and Schuster, *Naturwiss.*, 1937, **25**, 26 ; *Biochem. Z.*, 1937, **294** 188 ; Lohmann, *Angew. Chem.*, 1937, **50**, 221.

[2] Kinnersley and Peters, *J. Soc. Chem. Ind.*, 1937, **56**, 934 ; Stern and Hofer, *Science*, 1937, **85**, 485 ; Tauber, *J. Biol. Chem.*, 1938, **125**, 191.

dyes named the flavins, which have been extracted from various vegetable and animal sources. The flavins show strong vitamin B_2 activity,[1] and it is claimed that the flavin extracted from milk is identical with B_2.

(*b*) *Lactoflavin.*—Lactoflavin (I.) displays strong green fluorescence. When it is reduced by sodium hydrosulphide or hydrogen and platinum it takes up two atoms of hydrogen and is converted into leuco-lactoflavin, which readily reverts by atmospheric oxidation to the original compound. The leuco-compound is decomposed by light, and this, followed by oxidation and then treatment with cold alkali, yields the compound lumi-lactoflavin, $C_{13}H_{12}O_2N_4$ (III.). Lumi-lactoflavin, on treatment with boiling caustic soda solution, splits off urea to give a ketocarboxylic acid, $C_{12}H_{12}O_3N_2$ (IV.), and this by the action of heat loses carbon dioxide, leaving the compound $C_{11}H_{12}ON_2$ (V.). Lumi-lactoflavin has been synthesized and its structure confirmed.[2] The changes of lactoflavin through lumi-lactoflavin to 2-keto-1 : 6 : 7-trimethyl-1 : 2-dihydroquinoxaline (V.), are shown below.

$CH_2.(CHOH)_3.CH_2OH$ — N N — CH_3, CH_3 — CO — NH — N C=O

(I.) —— through the leuco-compd. ——→ (III.) Lumi-lactoflavin

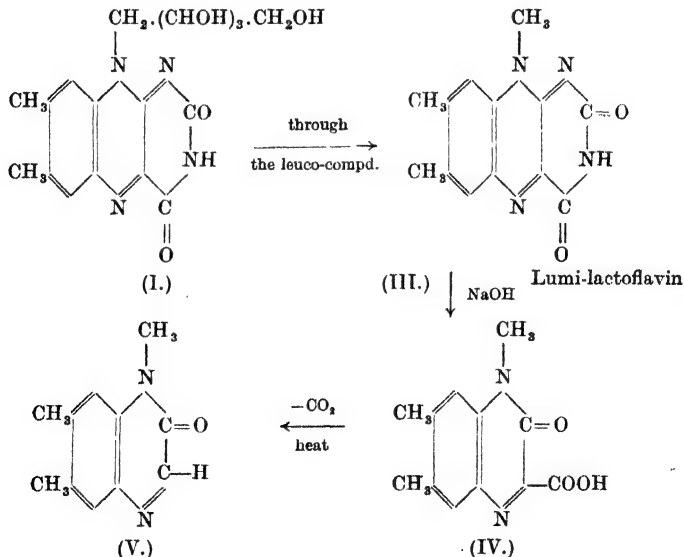
CH_3 — N N — CH_3, CH_3 — C=O — NH — N C=O

↓ NaOH

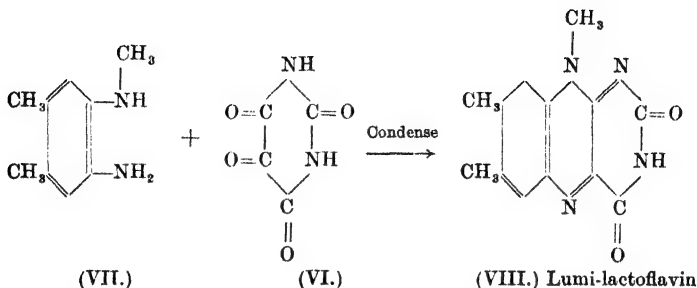
(IV.): CH_3 — N — CH_3, CH_3 — C=O — COOH — N

←— $-CO_2$, heat ——

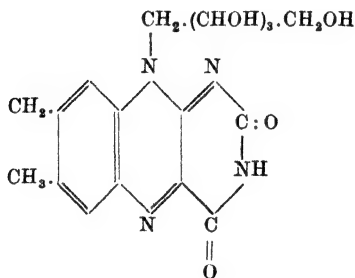
(V.): CH_3 — N — CH_3, CH_3 — C=O — C—H — N

---

[1] Kuhn, György and Wagner-Jauregg, *Ber.*, 1933, **66**, [B], 317, 576, 1034.
[2] Kuhn, Reinemund and Weygand, *Ber.*, 1934, **67**, [B], 1460.

The synthesis of lumi-lactoflavin has been accomplished as follows. The tetrahydrate of alloxan (VI.) and the hydrochloride of N-methyl-4 : 5-diamino-*o*-xylene (VII.) were condensed in water at 50°–60° C., the resulting product being 6 : 7 : 9 trimethyl flavin (VIII.), identical with lumi-lactoflavin from milk.

(VII.) + (VI.) —Condense→ (VIII.) Lumi-lactoflavin

Alkaline hydrolysis of the natural and synthetic lumi-lactoflavins yields the same quinoxaline derivative (IV.), and treatment with methyl sulphate leads in each case to the same tetra-methyl-flavin.

Lactoflavin forms a tetra-acetyl-derivative, and other evidence shows it to have the structure,

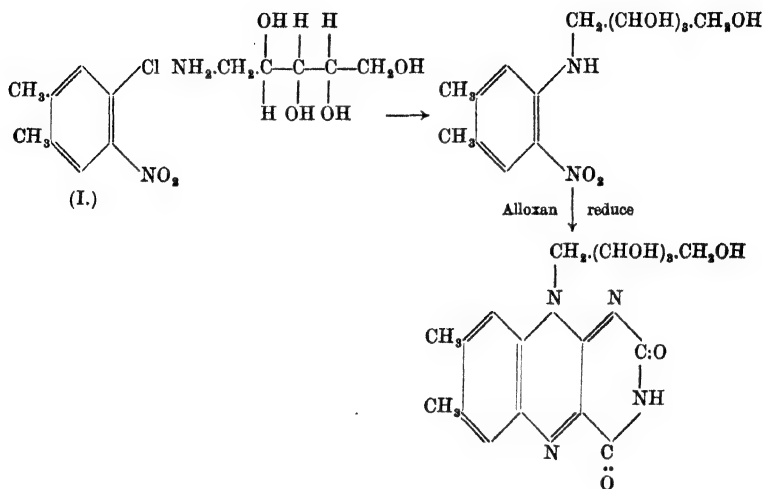
$CH_2.(CHOH)_3.CH_2OH$ (on N); $CH_2.$, $CH_3.$; C : O; NH

Several pentose derivatives were synthesized in order to determine the stereochemical positions of the hydroxyl groups in the side-chain. Kuhn [1] and his collaborators, starting from *l*-arabinose, prepared by reduction of the oxime, the corresponding amine, $NH_2.CH_2.(CHOH)_3.CH_2.OH$. This amine was

[1] Kuhn and Reinemund, *Ber.*, 1934, **67**, [B], 1932; Kuhn and Weygand, *ibid.*, 1939; *ibid.*, 1935, **68**, [B], 170.

condensed in the presence of pyridine with chloro-nitro-*o*-xylene (I.). The condensation product (II.) was reduced with stannous chloride in the presence of a large excess of alloxan, when a leuco-flavin was obtained. Oxidation by air converted the leuco-compound into the flavin. These steps are given below.

(I.) CH_3, CH_3, Cl, NO_2 + $NH_2.CH_2.C(H)(OH)—C(OH)(H)—C(OH)(H)—CH_2OH$ ⟶ CH_3, CH_3, $NH.CH_2.(CHOH)_3.CH_2OH$, NO_2

Alloxan ↓ reduce

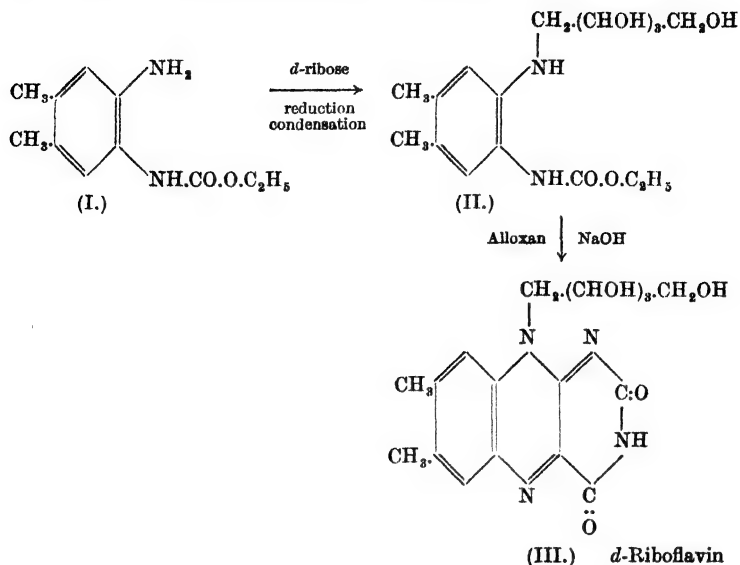
$CH_2.(CHOH)_3.CH_2OH$ on N; CH_3, CH_3; N, N, C:O, NH, N, C:O

This synthetic compound although behaving similarly to lactoflavin from natural sources in many ways has not its growth-promoting activity.

Karrer [1] and his collaborators have approached the problem by a different method of synthesis, and it is now agreed that the *d*-ribityl derivative is lactoflavin. When 1-amino-2-carbethoxy-amino-4 : 5-dimethyl-benzene (I.) is reduced in the presence of *d*-ribose, condensation takes place with the formation of the ribamine derivative (II.), and this substance is condensed with alloxan to give 6 : 7-dimethyl-9-[*d*-1′-ribityl]-*iso*-alloxazine (III.), which resembles the natural product very closely, and is biologically active.

[1] Karrer et al., *Ber.*, 1935, **68**, [B], 216.

CH_3, CH_3, NH_2, $NH.CO.O.C_2H_5$ (I.) —*d*-ribose, reduction, condensation→ $CH_2.(CHOH)_3.CH_2OH$, NH, CH_3, CH_3, $NH.CO.O.C_2H_5$ (II.)

Alloxan ↓ NaOH

$CH_2.(CHOH)_3.CH_2OH$, N, N, CH_3, CH_3, C:O, NH, N, C, O

(III.) *d*-Riboflavin

Other flavins such as the *l*-ribityl, xylityl and mannityl derivatives have been prepared but were found to have no biological activity.[1]

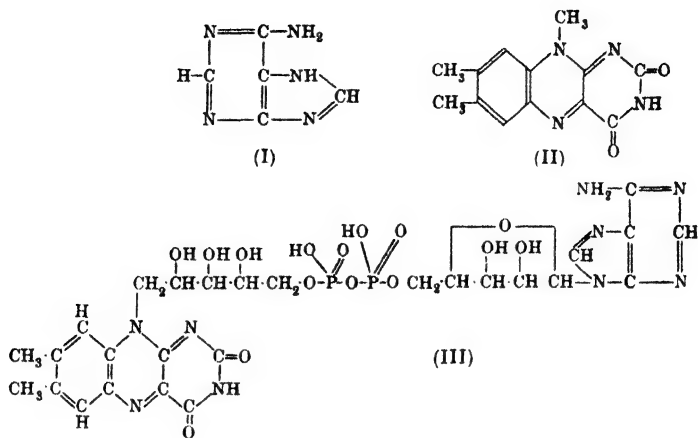
(*c*) *Riboflavin and Enzymes.*—A group of enzymes known as the flavoproteins have as their coenzyme a compound consisting of flavin-adenine-dinucleotide, which in conjunction with specific proteins forms different enzymes such as the *d*-aminoacid oxidase and the pyridine nucleotide oxidases. The flavin-adenine-dinucleotide compound on acid hydrolysis yields one molecular proportion of adenine (6-aminopurine) (I.) and lumiflavin (II.) by alkaline photolysis. The structure (III.) has been assigned to flavin-adenine-dinucleotide.[2]

[1] Karrer et al., *Helv. Chim. Acta*, 1935, **18**, 522; *Svensk Kem. Tidskr.*, 1935, **47**, 99.

[2] Warburg and Christian, *Biochem. Z.*, 1938, **298**, 150, 368.

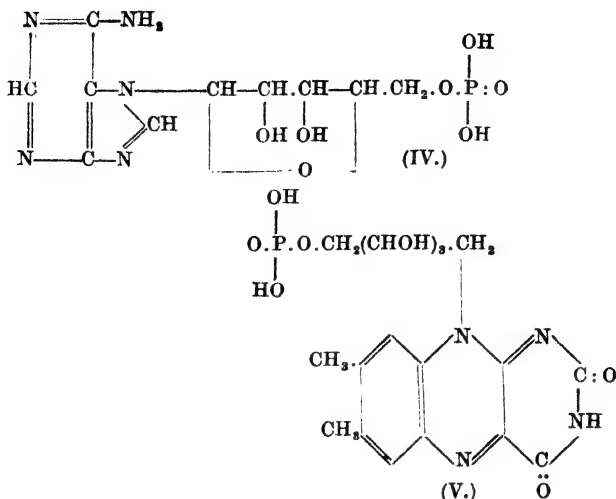
(I)

(II)

(III)

This mode of linkage of the different parts of the coenzyme was considered probable from the enzymic behaviour of the products of mild acid and alkaline hydrolysis. It is known that adenosine-5-phosphoric acid (muscle adenylic acid) (IV.) acts as an activator of the enzymic dephosphorylation of phosphoglyceric acid. This fact was utilized and the percentage hydrolysis of phosphoglyceric acid in enzyme systems measured in the presence of intact and hydrolysed flavin-adenine-dinucleotide, muscle adenylic acid and adenosine triphosphoric acid as activators. The experimental results pointed clearly to the presence of adenosine-5-phosphoric acid in the products of hydrolysis of the coenzyme. It was, therefore, concluded that this structure is present in the coenzyme flavin-adenine-dinucleotide. The flavin part of the molecule was investigated, after hydrolysis, in two enzyme systems which are quite differently affected by lactoflavin-5-phosphoric acid (V.). The results of these experiments indicated the production of lactoflavin-5-phosphoric acid from flavin-adenine-dinucleotide. Bearing in mind the fact that the coenzyme is very readily hydrolysed, especially in alkaline solution, the flavin-adenine-dinucleotide molecule may be built up from these two parts to give the structure (III.) : [1]

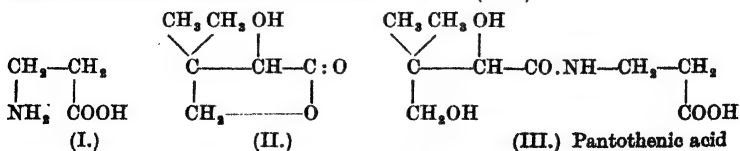
[1] Abraham, *Biochem. J.*, 1939, **33**, 543.

(IV.)

(V.)

Riboflavin has also been found in biological materials in the form of flavin nucleoside and flavin mononucleotide. It is evident that this development of the biochemistry of riboflavin is of major importance and considered along with parallel developments of the biochemistry of aneurin and nicotinic acid it throws a new light on the mode of action of the B vitamins.

4. *Pantothenic Acid*

The existence of this compound has been known for some years, but it eluded identification until 1940. A deficiency of the compound leads to degeneration in chicks, and it is necessary for the growth of certain micro-organisms. It has been obtained from many sources, the chief of which are liver, yeast, cereals and egg yolk. Pantothenic acid has the molecular formula $C_9H_{17}O_5N$. It yields β-alanine (I.) and α-hydroxy-β,β-dimethyl-γ-butyrolactone (II.) on hydrolysis and consequently it was assumed to be an amide of the structure (III.).[1]

(I.) (II.) (III.) Pantothenic acid

Further work proved this structure to be correct.

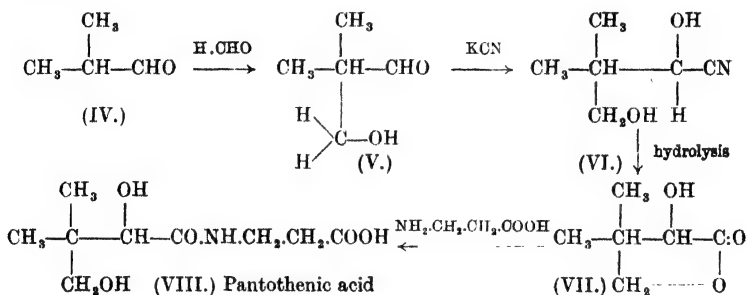
[1] Weinstock et al., *J. Amer. Chem. Soc.*, 1939, **61**, 1421; Mitchell et al., *ibid.*, 1940, **62**, 1776; Williams and Major, *Science*, 1940, **91**, 246.

The lactone (II.) was synthesized and condensed with β-alanine (I.), and the resulting compound (VIII.) was identical with natural pantothenic acid. The steps were as follows: α-methylpropionaldehyde (IV.) and formaldehyde were condensed in alkaline solution and yielded β-hydroxy-αα-dimethylpropionaldehyde (V.). From the aldehyde the cyanhydrin (VI.) was prepared and hydrolysed to give the racemic lactone (VII.). The sodium racemate in hot water was resolved by treatment with half an equivalent of quinine hydrochloride. The first crystallization of the quinine salt yielded the laevo-isomer of the lactone identical with that from pantothenic acid.[1] The laevo-lactone was then condensed with the sodium salt of β-alanine yielding pantothenic acid (VIII.).[2] The structures are given below.

$$\underset{\text{(IV.)}}{CH_3{-}\overset{\overset{\large CH_3}{|}}{C}H{-}CHO} \xrightarrow{H.CHO} \underset{\text{(V.)}}{CH_3{-}\overset{\overset{\large CH_3}{|}}{C}H{-}CHO \;\; (\text{with } {>}C{-}OH,\ H,\ H \text{ below})} \xrightarrow{KCN} \underset{\text{(VI.)}}{CH_3{-}\overset{\overset{\large CH_3}{|}}{\underset{\underset{\large CH_2OH}{|}}{C}}H{-}\overset{\overset{\large OH}{|}}{\underset{\underset{\large H}{|}}{C}}{-}CN}$$

(VI.) ↓ hydrolysis

$$\underset{\text{(VIII.) Pantothenic acid}}{CH_3{-}\overset{\overset{\large CH_3}{|}}{\underset{\underset{\large CH_2OH}{|}}{C}}{-}\overset{\overset{\large OH}{|}}{C}H{-}CO.NH.CH_2.CH_2.COOH} \xleftarrow{NH_2.CH_2.CH_2.COOH} \underset{\text{(VII.)}}{CH_3{-}\overset{\overset{\large CH_3}{|}}{\underset{\underset{\large CH_2}{|}}{C}}H{-}\overset{\overset{\large OH}{|}}{C}H{-}\underset{\underset{\large O}{|}}{C}{:}O}$$

(in VII. the CH_2 and O are joined by a dotted line)

5. *Nicotinic Acid and Coenzymes*

The biological importance of nicotinic acid and its amide is considerable: nicotinic acid has been identified as the human pellagra-preventing (P.P.) and dog "anti-black tongue" factor of the vitamin B complex; the acid is one of the widespread requirements of bacteria, and it has been established that nicotinic amide forms part of the molecules of the coenzymes codehydrogenase I. and codehydrogenase II. These two coenzymes play a part in a number of biological oxidations.

Codehydrogenase I. (diphosphopyridine nucleotide) breaks down on hydrolysis to yield one molecular proportion each of adenine and nicotinic amide, and two molecular proportions each of phosphoric acid and a pentose. Variations in the methods

[1] Stiller, Keresztesy, and Finkelstein, *J. Amer. Chem. Soc.*, 1940, **62**, 1779.
[2] Stiller, Harris, and Finkelstein, *ibid.*, 1940, **62**, 1785.

of hydrolysis yield other products. For example, mild acid hydrolysis gives rise to adenosine-5-phosphoric acid (I.). Structure (II.) has consequently been suggested for the coenzyme.[1]

Codehydrogenase II. (triphosphopyridine nucleotide) is in its chemical behaviour almost the same as codehydrogenase I., and has been obtained from it by enzyme action.[2] In physiological changes the nicotinic amide part of the coenzymes is the most reactive, taking up and losing hydrogen very rapidly.[3] The structure (III.) has been given to codehydrogenase II.[4]

It is not yet quite clear if the vitamin character of nicotinic acid is due solely to the necessity for it as part of these coenzyme molecules.

[1] Euler and Schlenk, *Z. physiol. Chem.*, 1937, **246**, 64.

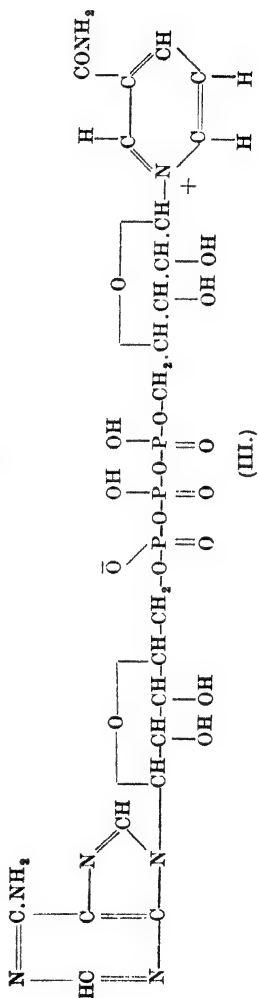
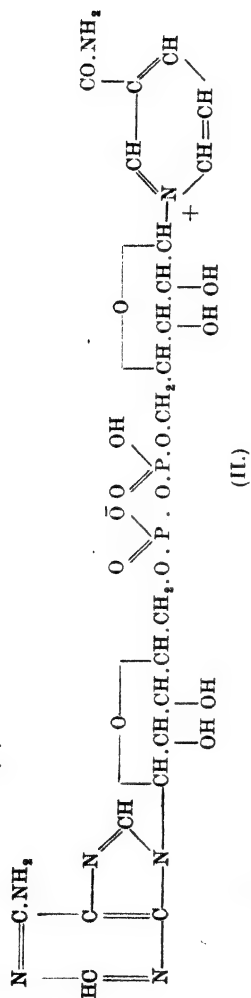
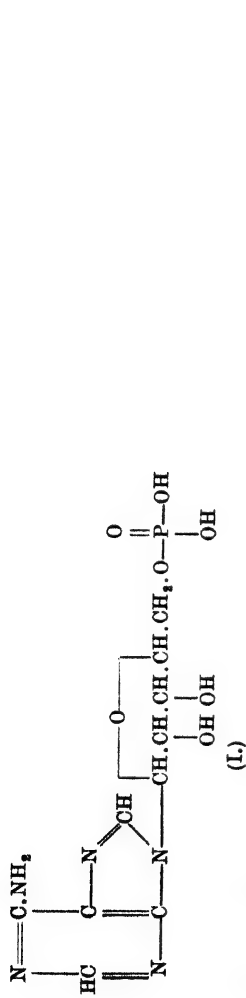
[2] Euler et al., *Z. physiol. Chem.*, 1937, **252**, 41 ; *Ber.*, 1938, **71**, 411 ; *Arkiv. Kemi Mineral. Geol.*, 1938, [B], **12**, 44.

[3] Schlenk, *Naturwiss.*, 1940, **28**, 46 ; Baumann and Stare, *Physiol. Rev.*, 1939, **19**, 353 ; Lutwak-Mann, *Biol. Rev.*, 1939, **14**, 399.

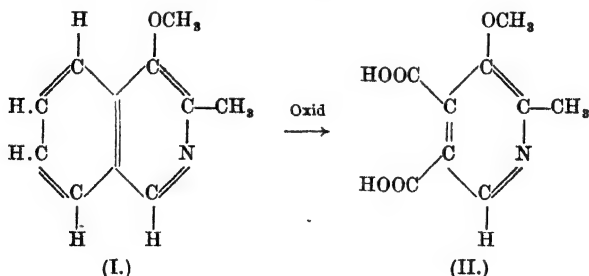
[4] Euler and Schlenk, *Z. physiol. Chem.*, 1937, **246**, 64 ; Warburg and Christian, *Biochem. Z.*, 1936, **287**, 291.

(I.)

(II.)

(III.)

6. *Vitamin* B_6 (*Adermin*)

This substance was isolated in a pure crystalline condition as the hydrochloride. Examination showed the base to be a comparatively simple pyridine derivative with the molecular formula $C_8H_{11}O_3N$. It contains one phenolic and two primary alcoholic hydroxyl groups and one methyl group.[1] A comparative study of the absorption spectra of the vitamin, three 3-hydroxypyridine derivatives and the 2- and 4-hydroxypyridines (α - and γ-pyridines) indicated that the phenolic hydroxyl of the vitamin was in the 3-position in the pyridine ring. Diazomethane, which is relatively indifferent to alcohols, yielded a monomethyl ether, $C_9H_{13}O_3N$ from the vitamin. This compound on oxidation with barium permanganate yielded a methoxymethylpyridine dicarboxylic acid (II.). As this acid gave no red colour with aqueous ferrous sulphate—a test for α-carboxylic acids of pyridine and quinoline—it was concluded that the primary alcoholic groups of the vitamin were attached at positions 4- and 5- of the ring.[2] This conclusion was confirmed and the position of the methyl group in the structure fixed by the preparation of the dibasic acid (II.) from 4-methoxy-3-methyl*iso*quinoline (I.) by oxidation.

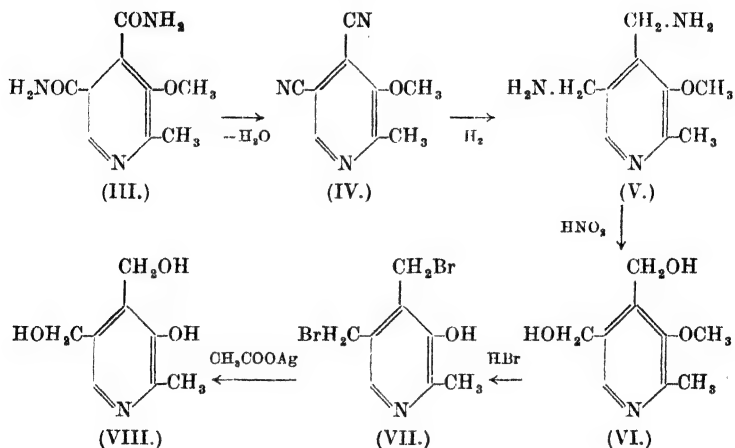
```
      H      OCH3                        OCH3
      |       |                            |
     C       C                    HOOC     C
   //  \   /  \\                      \  /  \\
H.C      C      C—CH3   Oxid           C      C—CH3
  |      ||     |       ---->          ||     |
H.C      C      N                      C      N
   \\  /   \  //                  HOOC/  \  //
     C       C                           C
     |       |                           |
     H       H                           H
        (I.)                            (II.)
```

The final stage in the proof of the structure of vitamin B_6 was the conversion of the dibasic acid (II.) into the vitamin in the following way. The acid (II.) was converted into its

[1] György, *J. Amer. Chem. Soc.*, 1938, **60**, 983; Kuhn and Wendt, *Ber.*, 1938, **71**, 780, 1118, 1534; Keresztesy and Stevens, *Proc. Exp. Biol. Med.*, 1938, **38**, 64; *J. Amer. Chem. Soc.*, 1937, **60**, 1267.

[2] Stiller, Keresztesy, and Stevens, *J. Amer. Chem. Soc.*, 1939, **61**, 1237.

amide (III.) and through this into the corresponding dicyano-compound (IV.), which on catalytic hydrogenation yielded the diaminomethyl derivative (V.). The action of nitrous acid converted the base into the alcohol (VI.). The alcohol was demethylated by the action of hydrogen bromide, and formed by the action of silver acetate on the dibromide (VII.) [1] vitamin B_6 (VIII.). The steps in the synthesis are :—

$CONH_2$ / H_2NOC– / –OCH_3 / –CH_3 / N (III.) $\xrightarrow{-H_2O}$ CN / NC– / –OCH_3 / –CH_3 / N (IV.) $\xrightarrow{H_2}$ $CH_2.NH_2$ / $H_2N.H_2C$– / –OCH_3 / –CH_3 / N (V.)

(V.) $\xrightarrow{HNO_3}$ CH_2OH / HOH_2C– / –OCH_3 / –CH_3 / N (VI.) $\xrightarrow{HBr}$ CH_2Br / BrH_2C– / –OH / –CH_3 / N (VII.) $\xrightarrow{CH_3COOAg}$ CH_2OH / HOH_2C– / –OH / –CH_3 / N (VIII.)

This structure has been confirmed by an independent synthesis of the vitamin.[2]

7. *The Biotins* (*Vitamin H*)

General.—Two biotins are known to which the structures (I.) and (II.) have been given. The former, referred to as β-biotin, has been isolated from liver and milk, and the latter, known as α-biotin, from egg yolk.[3] The two compounds have the same molecular formula, and have a certain resemblance in their

[1] Kuhn, Westphal, Wendt, and Westphal, *Naturwiss.*, 1939, **27**, 469 ; Kuhn et al., *Ber.*, 1939, **72**, 305–312.

[2] Harris, Stiller, and Folkers, *J. Amer. Chem. Soc.*, 1939, **61**, 1242, 1245, 3307.

[3] Kögl and Tönnis, *Z. physiol. Chem.*, 1936, **242**, 43 ; Vigneaud et al., *J. Biol. Chem.*, 1941, **140**, 643, 763 ; Melville et al., *J. Biol. Chem.*, 1942, **142**, 615.

atomic dispositions in the molecules. This may be seen more clearly by comparing structure (I.) with structure (III.).

(I.) β-Biotin

(II.) (III.) α-Biotin

The differences in structures are unexpected in view of the similarity in the biological properties of the two substances.

The biotins have been detected in a variety of foodstuffs and are essential for complete nutrition in many animals.

The Structures.—β-Biotin from liver and milk has been extensively examined and its synthesis accomplished. It has the molecular formula $C_{10}H_{16}O_3N_2S$, and its titration curve corresponded with that of a monocarboxylic acid.[1] When treated with barium hydroxide at 140° C. a diaminocarboxylic acid, $C_9H_{18}O_2N_2S$ (IV.) was isolated, and this compound reverted to β-biotin (I.) when treated with carbonyl chloride. This strongly suggests that β-biotin is a derivative of urea. The sulphur atom of β-biotin is very firmly bound in the molecule, and the formation of a sulphone by the action of hydrogen peroxide on β-biotin points to a thio-ether linkage in the molecule.[2] The diaminocarboxylic acid on treatment with alkaline permanganate or nitric acid yielded adipic acid (V.) from the products of oxidation, and as one of the carboxyls of adipic acid was shown to be the original acidic group of β-biotin the structure —$(CH_2)_4$—COOH must be attached as a side-chain to a carbon

[1] du Vigneaud et al., loc. cit., *Science*, 1940, **92**, 62, 609.

[2] Kögl and Pons, *Z. physiol. Chem.*, 1941, 269, 61; Kögl and de Man, *ibid.*, 1941, **269**, 82; Hofmann, Melville, and du Vigneaud, *J. Biol. Chem.*, 1941, **141**, 207; *Science*, 1941, **94**, 308.

atom of the remainder of the molecule.[1] Further, the reaction of the diaminocarboxylic with phenanthrenequinone to yield a dibenzoquinoxaline derivative (VI.) proves that the urea grouping present in β-biotin is part of a five-membered ring structure. This dibenzo-derivative was shown by means of its absorption spectrum curve to be a true quinoxaline (VI.) and not a dihydroquinoxaline derivative (VII.). In addition the formation of the quinoxaline indicates that the side-chain is not attached to a carbon directly joined to a nitrogen atom.[2]

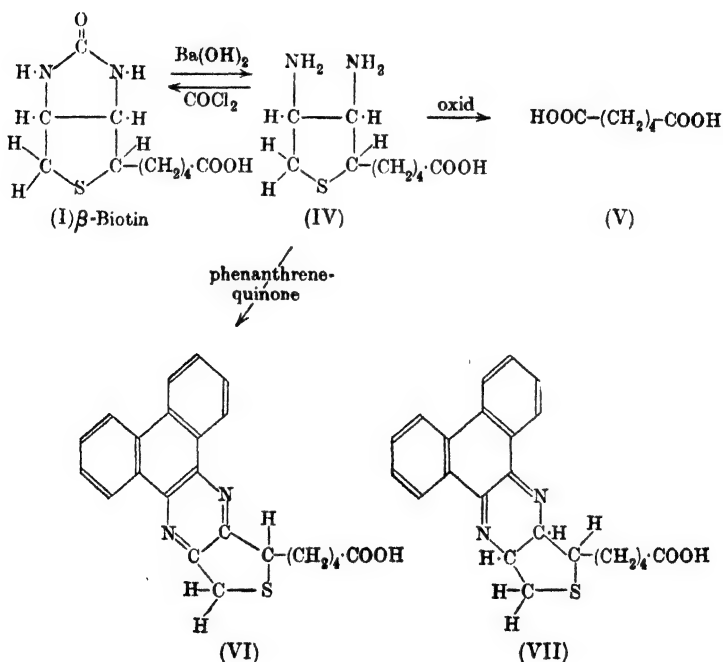
These changes and structures may be represented as follows,

$Ba(OH)_2$ ⇄ $COCl_2$; oxid

$HOOC-(CH_2)_4-COOH$

(I) β-Biotin (IV) (V)

phenanthrene-quinone

(VI) (VII)

An alternative structure for β-biotin is (VIII.), but the conversion of the diaminocarboxylic acid derived from β-biotin into the thiophen substituted valeric acid (IX.) rules this out

[1] Hofmann, Melville, and du Vigneaud, *J. Amer. Chem. Soc.*, 1941, **63**, 3237; 1942, **64**, 188; *J. Biol. Chem.*, 1942, **144**, 513.

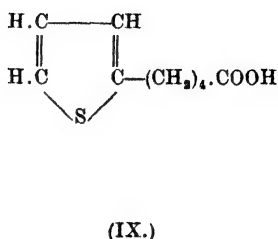
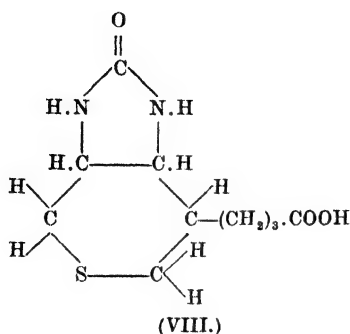
[2] Kilmer et al., *J. Biol. Chem.*, 1942, **145**, 495; Hofmann et al., *ibid.*, 1942, **145**, 503.

of court, leaving the structure (I.) as the best expression of the β-biotin molecule.[1]

```
              O
              ‖
              C
            /   \
        H.N       N.H
          |       |
        H.C ----- C.H
   H \  /           \  / H
       C              C—(CH2)3.COOH
   H /  \            // H
          S ------ C<
                     \ H

           (VIII.)

   H.C ——— CH
    ‖      ‖
   H.C     C—(CH2)4.COOH
     \    /
       S

      (IX.)
```

The Synthesis of β-biotin.—The structure given to liver and milk biotin from the study of its degradation products has been confirmed by the preparation of a synthetic compound identical in its properties with the product from natural sources. In this synthesis the starting materials were the sodium salts of *l*-cystine (X.) and chloroacetic acid (XI.). The condensation of these two compounds yielded β-(carboxymethylmercapto)-alanine (XII.). This substance was benzoylated and then esterified with the production of the compound (XIII.). These operations were followed by ring closure of the ester under the influence of sodium methoxide in solution in methyl alcohol. The sodium salt (XIV.) formed was converted into the keto-ester by the action of acid. Hydrolysis of the keto-ester followed by decarboxylation yielded the thiophen derivative (XV.). Condensation of this substance with the aldehyde (XVI.) introduced the valeric acid side-chain into the molecule. The keto-oxygen of this compound (XVII.) was replaced by the oxime group in the usual way with hydroxylamine. The oxime was reduced in acetic acid—acetic anhydride mixture with zinc dust. One of the products was the acetamido-derivative (XVIII.).

Hydrogenation of this compound with palladium as the catalyst yielded two racemates of the saturated diamidothiophen derivative (XIX.). These were hydrolysed, acidified with sul-

[1] Melville et al., *J. Biol. Chem.*, 1942, **146**, 487 ; du Vigneaud et al. ; *ibid.*, 1942, **146**, 475 ; Mozingo et al., *J. Amer. Chem. Soc.*, 1943, **65**, 1013.

phuric acid and finally treated with carbonyl chloride. Two racemates were isolated, one of which was *dl*-β-biotin (XX.).

dl-β-Biotin was then resolved through its esters with *l*-mandelic acid to give β-biotin.[1] The following scheme shows the structural steps in the synthesis.

$Na{\cdot}S{\cdot}CH_2{\cdot}CH(NH_2){\cdot}COONa$ (X) + $Cl{\cdot}CH_2{\cdot}COONa$ (XI) → $H{\cdot}C(NH_2){\cdot}COOH$, CH_2–S–$CH_2{\cdot}COOH$ (XII) —(a) C_6H_5COCl; (b) C_2H_5OH→ $H{\cdot}C(NH{\cdot}COC_6H_5){\cdot}COOC_2H_5$, CH_2–S–$CH_2{\cdot}COOC_2H_5$ (XIII)

(XIII) —CH_3ONa→ $NH{\cdot}COC_6H_5$; $H{\cdot}C$—$C{\cdot}ONa$; CH_2 $C{\cdot}COOC_2H_5$; S (XIV) —(a) acid (b) hydrolysis (c) decarboxylation→ $NH{\cdot}COC_6H_5$; $H{\cdot}C$—$C{:}O$; CH_2 CH_2; S (XV) —H $O{:}C{\cdot}(CH_2)_3COOCH_3$ (XVI)→ $NH{\cdot}CO{\cdot}C_6H_5$; $H{\cdot}C$—$C{:}O$; CH_2 $C{:}CH(CH_2)_3{\cdot}COOCH_3$; S (XVII)

(XVII) —(a) oxime formation (b) reduction→ $NH{\cdot}CO{\cdot}C_6H_5$; $H{\cdot}C$—$C{\cdot}NH{\cdot}CO{\cdot}CH_3$; CH_2 $C{\cdot}(CH_2)_4{\cdot}COOCH_3$; S (XVIII) —$H_2$, Pd→ C_6H_5 CH_3; CO CO; NH NH; $H{\cdot}C$—$C{\cdot}H$; CH_2 $C{\cdot}(CH_2)_4{\cdot}COOCH_3$ (H); S (XIX) —(a) hydrolysis (b) sulphuric acid (c) carbonyl chloride→ O; C; NH NH; $H{\cdot}C$—$C{\cdot}H$; CH_2 $C{\cdot}(CH_2)_4$ COOH (H); S (XX) β-Biotin

α-Biotin isolated from egg-yolk has provisionally been given the structure (XXI.) from the study of some of its products of degradation. Like the β-compound α-biotin was shown to contain a cyclic urea grouping and the sulphur atom in a cyclic system.[2]

When α-biotin (XXI.) was hydrolysed it yielded the diamino-acid (XXII.), which on oxidation with lead tetra-acetate was converted into the aminoaldehyde (XXIII.). Further oxidation with potassium permanganate yielded the aminocarboxylic

[1] Harris et al., *Science*, 1943, **97**, 447; *J. Amer. Chem. Soc.*, 1944, **66**, 1756, 1757, 1800.

[2] Kögl et al., *Z. physiol. Chem.*, 1941, **269**, 81.

acid (XXIV.). Esterification of the acid in hot solution gave rise to the unsaturated ester (XXV.). Hydrolysis of the ester followed by oxidation with permanganate produced the sulphonic acid (XXVI.).[1] The structure of this final product was fully proved by its conversion into αβ-dimethylbutyric acid and by its synthesis.

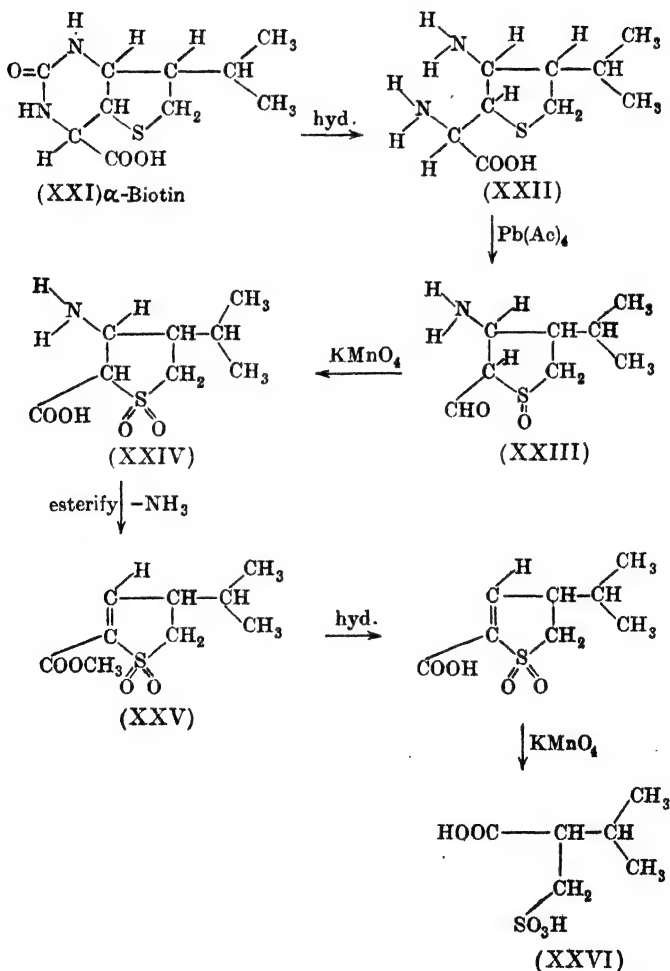
The scheme of structures is as follows :—

(XXI) α-Biotin —hyd.→ (XXII)

(XXII) —$Pb(Ac)_4$→ (XXIII)

(XXIII) —$KMnO_4$→ (XXIV)

(XXIV) —esterify, $-NH_3$→ (XXV)

(XXV) —hyd.→ —$KMnO_4$→ (XXVI)

[1] *Idem, ibid.*, 1942, **276**, 63 ; 1943, **279**, 121 ; 1944, **281**, 65.

When the methyl ester of α-biotin was converted into its sulphone (XXVII.) and then hydrolysed a diamino-dibasic acid (XXVIII.) was produced. These changes may be formulated as,

```
      H                                           H
      N    H    H  CH3                            N    H    H  CH3
    /   \  /    / /                             /   \  /    / /
O:C      C----C--CH            oxid.        O:C      C----C--CH
  |      | H  |   \CH3        ------>         |      | H  |   \CH3
 HN     C    CH2                             HN     C    CH2
   \   / \   /                                 \   / \   /
    C     S                                     C     S
   / \                                         / |   // \\
  H   COOCH3                                  H  |   O   O
                                                 COOCH3   (XXVII)
                                                    |
                                                    | hyd
                                                    v
                                          H
                                           \N    H    H  CH3
                                          H/  \  /    / /
                                               C----C--CH
                                        H      |    |   \
                                         \N   CH2  CH2   CH3
                                        H/ \  /    /
                                            C    SO3H
                                          H/|
                                            COOH  (XXVIII)
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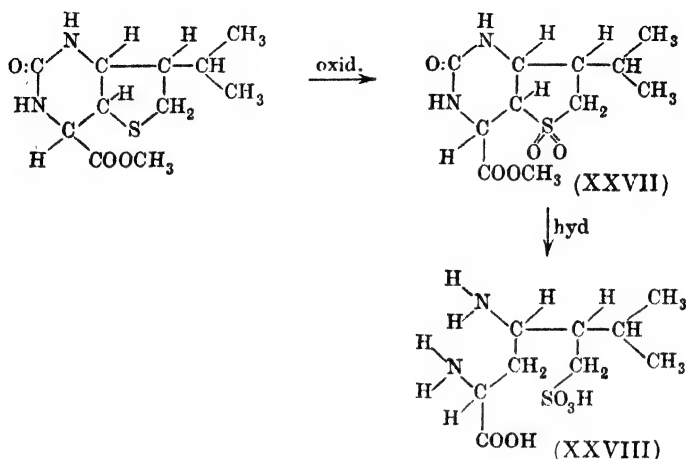

These interpretations of the changes point to α-biotin having a pyrimidine ring structure in the molecule, and to the sulphur atom being in a separate five-membered cyclic arrangement. Final judgment, however, must be suspended until this structure has been confirmed by synthesis.

D.—Vitamin C (*l*-Ascorbic Acid)

1. *Introductory*

It has been known for a long time that scurvy is definitely due to the absence from the diet of some vitamin. The discovery that guinea pigs develop the disease when deprived of green foodstuffs and fed on grain and water, led to the investigation of the distribution and behaviour of the antiscorbutic vitamin. The vitamin is present in a great variety of foodstuffs, and is relatively abundant in fresh green vegetables and fruit juices.[1] In the chemical study of the vitamin the most noticeable property

[1] *Vitamins: A Survey of Present Knowledge. Medical Research Council*, **1932.**

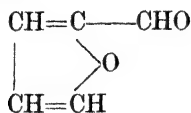
was its strong reducing action, and it was suggested that it might be identical with the strongly reducing hexuronic acid found in the adrenals of animals and in many fruit juices. This focused attention on hexuronic acid, and it was found to have powerful anti-scorbutic properties. The general opinion was then reached that hexuronic acid was vitamin C, and for this reason the acid was renamed ascorbic acid.

2. *Properties of Vitamin C*

Vitamin C is very sensitive to oxidizing agents [1]; inactivation occurs rapidly in alkaline solution in the presence of air. The vitamin dissolves readily in water and in alcohol, but is insoluble in butyl alcohol and in light petroleum. It is precipitated by basic lead acetate, and this property is made use of in the concentration of the vitamin.

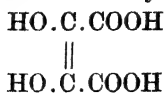
3. *Constitution of l-Ascorbic Acid*

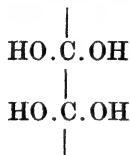
l-Ascorbic acid has the molecular formula $C_6H_8O_6$, and behaves as a weak acid, yielding salts of the type $C_6H_7O_5M$, but it cannot be converted into a lactone. It reacts readily with phenylhydrazine, indicating the presence of a carbonyl group. The colour reactions with ferric chloride and sodium nitroprusside, and the nature of the ultra-violet absorption spectrum point to the presence of an enolic group. The fact that treatment with boiling hydrochloric acid gives a quantitative yield of furfuraldehyde,

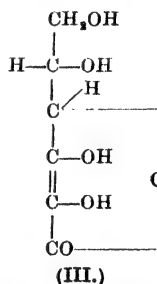
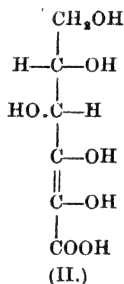
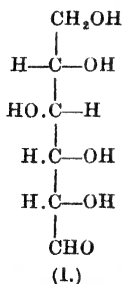
```
CH=C——CHO
|    \
|     >O
|    /
CH=CH
```

shows that five of the carbon atoms are present as an unbranched chain.[2] When *l*-ascorbic acid is oxidized by iodine in aqueous acid solution two molecules of hydriodic acid are formed, and the ascorbic acid takes up two oxygen atoms and two hydrogen atoms (2-OH). The compound formed can be quantitatively re-converted into ascorbic acid by reducing agents. There is

[1] Szent-Györgyi, *Biochem. J.*, 1928, **22**, 1387.
[2] Cox, Hirst and Reynolds, *Nature*, 1932, **130**, 888.

strong resemblance between some of the chemical and physical properties of ascorbic acid and dihydroxy-maleic acid,

```
HO.C.COOH
   ||
HO.C.COOH
```

and the unsaturated grouping of the latter is postulated in ascorbic acid. The first product (IV.) of the oxidation of ascorbic acid by aqueous iodine is regarded as containing the grouping

```
   |
HO.C.OH
   |
HO.C.OH
   |
```

by oxidation at the double bond. Further oxidation yields oxalic acid and *l*-threonic acid [1] (trihydroxy-butyric acid) (VI.) Ascorbic acid, then, is derived from *l*-gulose (I.), and may be represented as the lactone (III.) of the unsaturated acid (II.).

```
   CH2OH          CH2OH          CH2OH
    |              |              |
 H—C—OH         H—C—OH         H—C—OH
    |              |              |  /H
 HO.C—H         HO.C—H            C ------
    |              |              |       |
  H.C—OH           C—OH           C—OH    |
    |              ||             ||      O
  H.C—OH           C—OH           C—OH    |
    |              |              |       |
   CHO            COOH            CO------
   (I.)           (II.)          (III.)
```

The steps in the formation of oxalic and *l*-threonic acids from ascorbic acid may now be represented as :

```
 CH2OH              CH2OH                  CH2OH             CH2OH
  |                  |                      |                 |
 HC—OH            H—C—OH       −2H2O      H—C—OH            H.C—OH
  |  /H              |  /H     ----->       |                 |
  C ------  Oxid     C ------            HO.C—H    ----->  HO.C—H
  |       | ---->    |       |              |                 |
  C—OH    |       HO.C.OH    |              C:O              COOH
  ||      O          |       O  <-----      |
  C—OH    |       HO.C.OH    |   +2H2O      C:O              COOH
  |       |          |       |              |                 |
  CO------           CO------              COOH              COOH
                    \_________ in equilibrium. _________/
 (III.)             (IV.)                  (V.)              (VI.)
```

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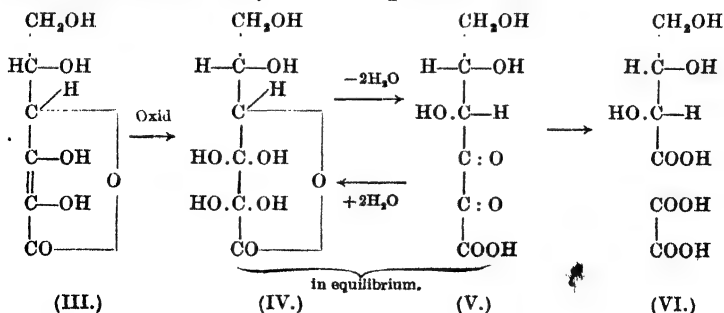
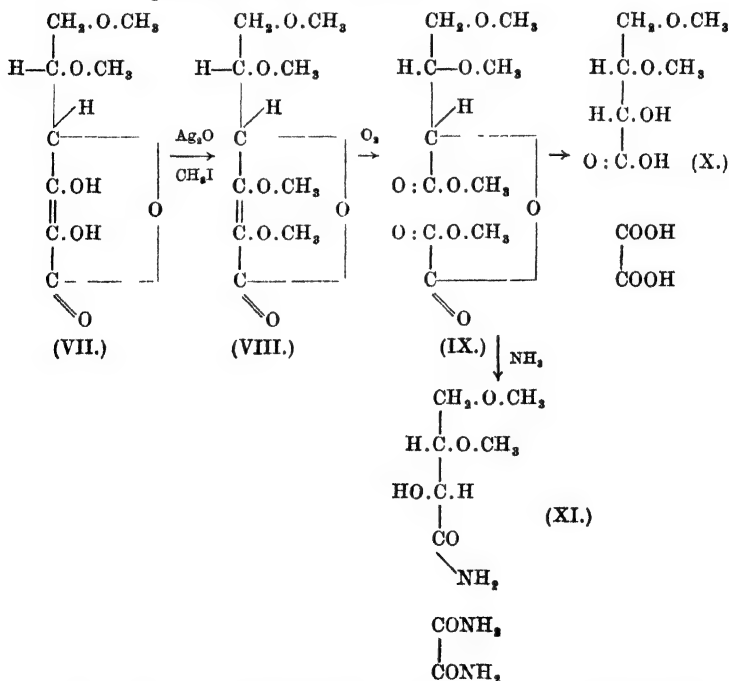
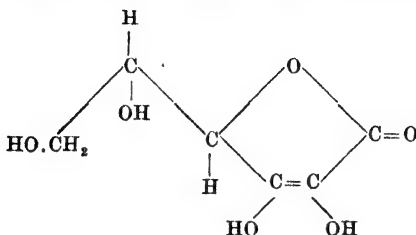

[1] Cox, Hirst and Reynolds, *Nature*, 1932, **130**, 888.

The acidic properties of *l*-ascorbic acid are due to an activated —CHOH group adjacent to a carbonyl group, and not to a carboxyl group. Ascorbic acid (III.) has been given the furanose type of lactone ring, and this was proved correct by a study of its methylated derivatives.[1] A dimethyl-derivative (VII.) is produced from ascorbic acid by the action of diazomethane, and further methylation by silver oxide and methyl iodide yields a tetramethyl-derivative (VIII.). This tetramethyl-ascorbic acid is oxidized by ozone to yield methyl-3 : 4-dimethyl-*l*-threonate substituted in position 2 by a methyl oxalate residue (IX.), which, on hydrolysis, yields oxalic acid and 3 : 4-dimethyl *l*-threonic acid (X.). Treatment of the ester (IX.) with ammonia produces oxamide and 3 : 4-dimethyl-*l*-threonamide (XI.) as the principal products. The ascorbic acid molecule, therefore, contains a five-membered lactone ring, as the oxidation product 3 : 4-dimethyl-*l*-threonic acid has a free hydroxyl group in the α-position.

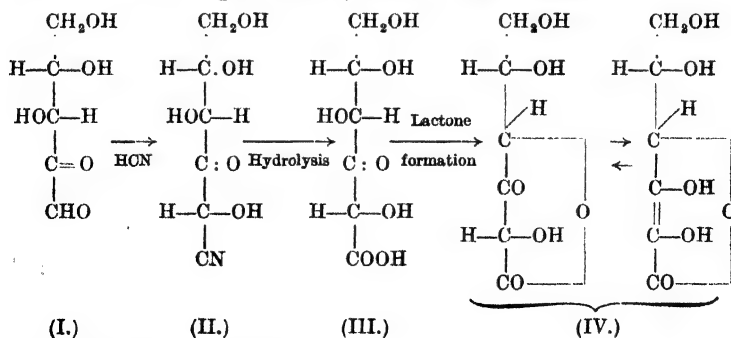
The changes are formulated as follows :

[1] Hirst, Percival and Smith, *Nature*, 1933, 131, 617.

Crystallographic and X-ray examinations of *l*-ascorbic acid point to the molecule containing double bonds and having a ring structure with fewer groups projecting out of the plane of the ring than a normal carbohydrate.[1] A flat structure is also indicated and the molecule may be represented as

4. *Synthesis of l-Ascorbic Acid*

l-Xylose was prepared from *d*-galactose, and the osone (I.) in water treated with a solution of calcium chloride and potassium cyanide in an atmosphere of nitrogen.[2] The osone adds on hydrogen cyanide (II.), and this is followed by immediate hydrolysis. On concentration of the solution under reduced pressure in an atmosphere of carbon dioxide a thick syrup is obtained. The syrupy pseudo-ascorbic acid (III.) thus obtained, after purification, is dissolved in hydrochloric acid and subjected to prolonged digestion at 45°–50° C. in an inert atmosphere. On removal of impurities crystalline *l*-ascorbic acid (IV.) is obtained. The steps from *l*-xylosone are as follows :

```
 CH2OH          CH2OH           CH2OH            CH2OH            CH2OH

H—C—OH        H—C.OH          H—C—OH           H—C—OH           H—C—OH
  |             |               |                |                |
 HOC—H         HOC—H           HOC—H  Lactone    | /H             | /H
  |    ——→      |    ————→      |     ————→      C------          →  C------
 C=O   HCN     C : O Hydrolysis C : O formation  |      |       ←   |      |
  |             |               |                CO     |           C—OH   |
 CHO          H—C—OH          H—C—OH             |      O           ||     C
                |               |              H—C—OH   |           C—OH   |
                CN              COOH             |      |           |      |
                                                 CO------           CO------

 (I.)           (II.)           (III.)                    (IV.)
```

[1] Cox, *Nature*, 1932, **130**, 205.

[2] Haworth et al., *J.S.C.I.*, 1933, **52**, 645 ; *J.*, 1933, 1419 ; Reichstein, Grüsoner, and Oppenauer, *Helv. Chim. Acta*, 1933, **16**, 561, 1019 ; 1934, **17**, 311, 510.

The formula put forward as the result of the study of the oxidation and other products of natural *l*-ascorbic acid is strongly supported by this synthesis.

E.—The Vitamins of the D Group

1. *Introductory*

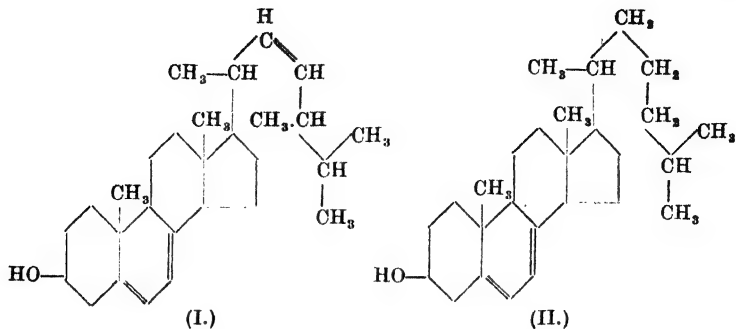
Vitamins of the D group have the specific function of controlling the deposition of calcium and phosphorus in tissues, and a deficiency of a D vitamin in the diet leads to dental caries and to defective bone formation, such as rickets. Absence of the vitamin, however, is not the only factor concerned in the causation of rickets; the mineral constituents of the diet play a part. A vitamin D is also necessary for growth since young animals deprived of it cease, after a time, to increase in weight, and resume growth when it is added to the diet. It is an important, and now well-known, fact that ultra-violet rays have a stimulating effect on calcification.[1] Young rats, kept on a diet deficient in a vitamin D, which would ordinarily cause rickets, remain free from the disease if they are exposed to sunlight or the rays of a mercury quartz lamp. Foodstuffs have been found to respond to irradiation. A normally inert substance like cottonseed oil after exposure to ultra-violet light acquired antirachitic potency.[1] The mechanism by which ultra-violet rays exert their antirachitic action is connected with the presence of a vitamin precursor (provitamin) in the animal and human skin or in the blood circulating near the skin surface. Two of these natural provitamins are known with certainty, ergosterol (I.) giving rise to calciferol or vitamin D_2,[2] and 7-dehydrocholesterol (II.) the parent substance of vitamin D_3. Ergosterol is the chief sterol of yeast and fungi and was first isolated from ergot. 7-Dehydrocholesterol is a constituent of the animal body and is the precursor of vitamin D_3, which the body makes for itself by means of the sun's rays.[3] Vitamin D_3 itself has been isolated from halibut- and tunny-liver oils.[4]

[1] Hess, *Amer. J. of Diseases of Children*, 1924, **28**, 517.

[2] Rosenheim and Webster, *Biochem. J.*, 1927, **21**, 127, 289; Windaus and Hess, *Nachr. ges. Wiss. Gottingen*, 1927, **175**, 84.

[3] Windaus and Bock, *Z. physiol. Chem.*, 1937, 245, 168.

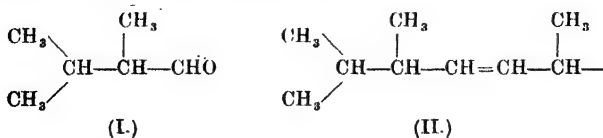
[4] Brockmann, *Z. Physiol. Chem.*, 1937, **245**, 96; Brockmann and Busse, *Naturwiss.*, 1938, **26**, 122; *Z. physiol. Chem.*, 1938, **256**, 252.

(I.) (II.)

An antirachitic substance derived from 22-dihydroergosterol is known as vitamin D_4. A number of other sterols can be transformed to show antirachitic effects. " Vitamin D " is more sparsely distributed in foodstuffs than other vitamins; this, however, is partially compensated for by the direct influence of sunlight on the skins of animals. The chief sources of " vitamin D " are milk, butter, eggs, fresh green vegetables and fish-liver oils.

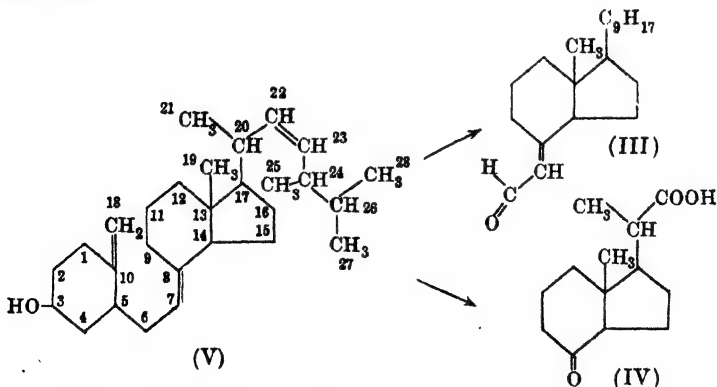
2. *The Structure of Calciferol (Vitamin D_2)*

Calciferol, $C_{28}H_{44}O$, has been characterized as unsaturated and containing a secondary alcoholic group. It readily forms crystalline esters with 3 : 5-dinitrobenzoyl chloride and with *p*-nitrobenzoyl chloride; and it was by means of the former compound that calciferol was isolated in a pure condition from the crude products of irradiation.[1] When calciferol was reduced by sodium and alcohol it yielded a dihydrocalciferol and on complete hydrogenation took up four molecules of hydrogen. On oxidation calciferol yielded methyl *iso*propyl acetaldehyde (I.), which has also been obtained by oxidation from ergosterol. It is probable then that the side chain (II.) of the calciferol molecule is the same as in ergosterol.

$$(CH_3)_2CH{-}CH(CH_3){-}CHO \quad \text{(I.)}$$

$$(CH_3)_2CH{-}CH(CH_3){-}CH{=}CH{-}CH(CH_3){-} \quad \text{(II.)}$$

[1] Askew, Bruce et al., *Nature*, 1931, **128**, 758.

It was thought for some time that calciferol contained the four-ring system of the sterols, but on further investigation this was shown to be incorrect. The first clue that calciferol did not contain the sterol ring framework was obtained when it was observed that the vitamin did not yield 3′-methyl-1 : 2-*cyclo*-pentenophenanthrene on dehydrogenation with selenium. This was followed up by an examination of tachysterol, which immediately precedes calciferol in the irradiation series (see page 77). The citraconic anhydride compound of tachysterol acetate on catalytic hydrogenation behaved like dehydroergosterol, which is known to contain four ethylenic linkages, after similar treatment. To accommodate four double carbon bonds it was suggested that the ring system of tachysterol was open between carbon atoms 9 and 10.[1] A quantitative study of the action of perbenzoic acid and microcatalytic hydrogenation of calciferol showed that the vitamin also had four ethylenic linkages in the molecule.[2] Oxidation of calciferol with either chromic anhydride or potassium permanganate yielded a compound, $C_{21}H_{34}O$ (III.), which was shown to be an αβ-unsaturated aldehyde. When calciferol was ozonized formaldehyde and a keto-acid, $C_{13}H_{20}O_3$ (IV.), were obtained.[3] The formation of these oxidation products is strong evidence that the calciferol molecule is open between carbon atoms 9 and 10, and has ethylenic linkages between carbon atoms 7–8 and 10–18. The partial structure (V.) may now be given to calciferol.

(V) (III) (IV)

[1] Lettré, *Annalen*, 1934, **511**, 280.

[2] Kuhn and Möller, *Angew. Chem.*, 1934, **47**, 145; Reichel and Deppe, *Z. physiol. Chem.*, 1936, **239**, 143.

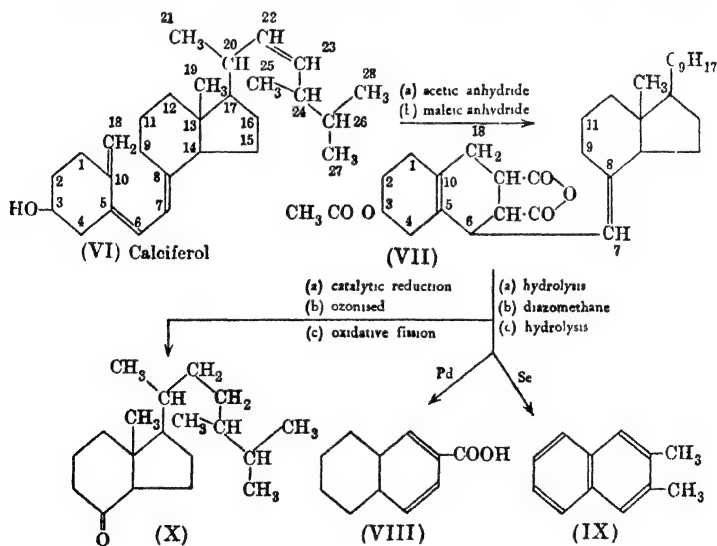
[3] Heilbron et al., *Nature*, 1935, **135**, 1072; *J.*, 1936, 905.

The positions of these two ethylenic linkages were confirmed and the remaining double carbon bond shown to be between carbon atoms 5 and 6 in the following way. Calciferyl acetate was converted into its maleic anhydride addition compound (VII.) and then, after hydrolysis, acted upon by diazomethane to give α-calciferyl acetate dimethyl maleate. This compound in its turn was hydrolysed to α-calciferyl maleic acid, which was dehydrogenated by palladized charcoal to yield β-naphthoic acid (VIII.). When selenium was used in place of palladium the product was 2 : 3-dimethylnaphthalene (IX.). Finally, α-calciferyl acetate dimethyl maleate was catalytically converted into its dihydro-derivative and ozonized. This was followed by oxidative fission of the ozonide which yielded the ketone (X.).[1] These changes can only be explained by placing the three ethylenic linkages between carbon atoms 18–10, 5–6, and 7–8 (VI.). Consequently, calciferol is given the structure (VI.).

The scheme of structures shows the steps in these changes.

(VI) Calciferol → (a) acetic anhydride (b) maleic anhydride → (VII)

(VII) → (a) catalytic reduction (b) ozonised (c) oxidative fission → (X)

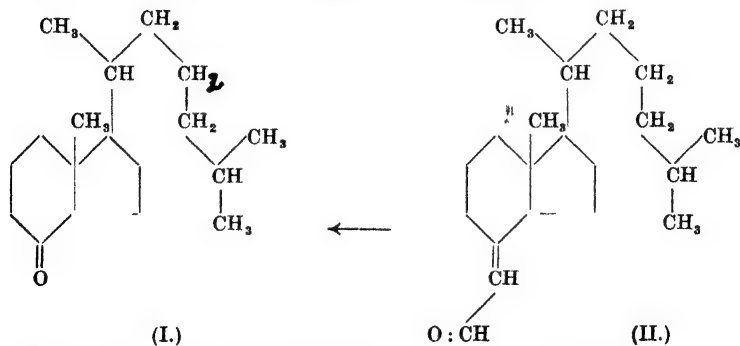
(VII) → (a) hydrolysis (b) diazomethane (c) hydrolysis → Pd → (VIII); Se → (IX)

3. *The Structure of Vitamin D_3*

When it became evident that calciferol was not the only vitamin of the D group, and that 22-dihydroergosterol could give

[1] Windaus and Thiele, *Annalen*, 1935, **521**, 160.

rise to a compound having antirachitic properties, it was suggested that the provitamin normally present with cholesterol was the substance now known as 7-dehydrocholesterol (IV.).[1] This deduction was fully justified when this compound, synthetically prepared from cholesterol through the 7-keto-derivative, on irradiation gave a substance with powerful antirachitic properties.[2] This was followed by the isolation of the provitamin 7-dehydrocholesterol and the vitamin D_3 from natural sources. Chemical examination of vitamin D_3 prepared from 7-dehydrocholesterol by irradiation and isolated from tunny-liver oil showed it to be closely related to calciferol.[3]

The irradiation of vitamin D_3 yielded lumisterol$_3$, $C_{27}H_{44}O$ and tachysterol$_3$, which very closely resembled lumisterol and tachysterol respectively in their chemical properties.[4] Vitamin D_3 isolated from irradiated 7-dehydrocholesterol on ozonization gave a ketone $C_{18}H_{32}O$, which, from analogy with the ketone obtained from calciferol has been given the structure (I.).[5] Natural vitamin D_3, isolated from tunny-liver oil, on ozonization yielded formaldehyde, an aldehyde $C_{20}H_{34}O$ and the ketone, $C_{18}H_{32}O$, identical with the ketone obtained from irradiated 7-dehydrocholesterol. The aldehyde $C_{20}H_{34}O$ and the ketone $C_{18}H_{32}O$ are obviously the counterparts of those obtained from calciferol. The aldehyde may be formulated as (II.):

(I.) ← (II.)

[1] Callow, *Sci. J., Rot. Coll. Sci.*, 1934, **4**, 41.

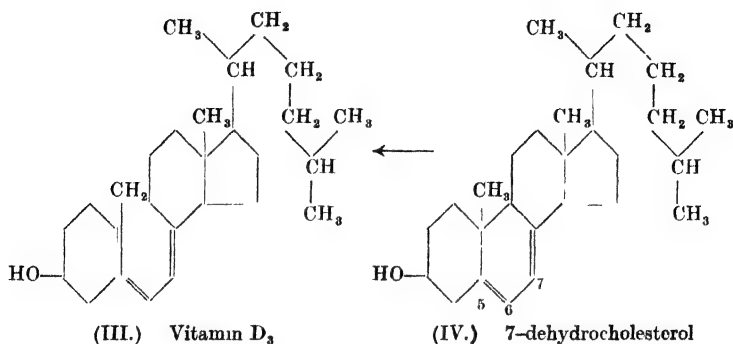
[2] Windaus, Lettré, and Schenk, *Annalen*, 1935, **520**, 98; Schenk, Buchholz and Wiese, *Ber.*, 1936, **69**, 2696.

[3] Brockmann and Busse, *Naturwiss.*, 1938, **26**, 122; *Z. physiol. Chem.*, 1938, **256**, 252.

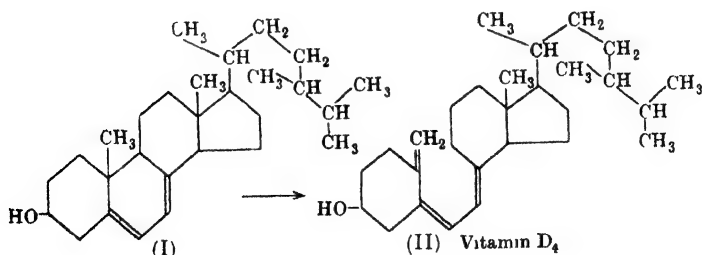
[4] Schenck, *Naturwiss.*, 1937, **25**, 159; Windaus, Deppe and Wunderlich, *Annalen*, 1937, **533**, 118.

[5] Brockmann and Busse, *loc. cit.*

In the absence of any contradictory evidence vitamin D_3 may therefore be given the structure (III.), bringing it into line with calciferol.

(III.) Vitamin D_3 (IV.) 7-dehydrocholesterol

4. *The Structure of Vitamin D_4*

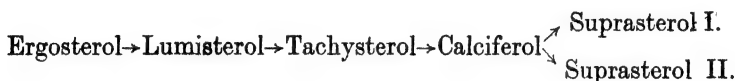
This substance has been isolated in the form of its 3 : 5-dinitrobenzoate from the irradiation products of 22 : 23-dihydroergosterol (I.) and some of the physical constants of the vitamin recorded.[1] In addition, irradiation under varying conditions yielded lumisterol$_4$, tachysterol$_4$, and a suprasterol$_4$. Tachysterol$_4$ proved to be identical with the substance obtained by the hydrogenation of tachysterol.[2] It is assumed that these different irradiation products are formed in the same way as the corresponding compounds from ergosterol and 7-dehydrocholesterol, and consequently the structure (II.) is given to vitamin D_4.

(I) (II) Vitamin D_4

[1] Windaus and Trautmann, *Z. physiol. Chem.*, 1937, **247**, 185.

[2] Windaus and Güntzel, *Annalen*, 1939, **538**, 120.

5. *The Products of Irradiation of Ergosterol*

As ergosterol was for some time thought to be the sole precursor of vitamin D it was extensively examined, and the information obtained proved to be the key to the interpretation of the results of the photochemical investigation of 7-dehydrocholesterol and 22–23-dihydroergosterol. Irradiation of ergosterol yielded a complex resinous mixture which contained calciferol. For a time this resinous material defied separation, but finally crystalline substances were obtained by distillation in high vacuum combined with fractional condensation.[1] In addition to this method, the application of Diel's reaction with maleic or citraconic anhydride to the products of irradiation also permits the isolation of crystalline substances. The process of isomerization of ergosterol by ultra-violet light occurs in stages, and five well-characterized isomers have been obtained. The steps are,

$$\text{Ergosterol} \rightarrow \text{Lumisterol} \rightarrow \text{Tachysterol} \rightarrow \text{Calciferol} \begin{cases} \nearrow \text{Suprasterol I.} \\ \searrow \text{Suprasterol II.} \end{cases}$$

The compounds are placed in this order as prolonged irradiation of the suprasterols brings about no further change, and these two substances along with another product, toxisterol, which has not yet been isolated in a pure condition, are regarded as the end-products of irradiation of ergosterol; calciferol yields the suprasterols, and irradiated lumisterol gives rise to a mixture of tachysterol, calciferol, and the suprasterols. As irradiation proceeds, the strong laevo-rotation of ergosterol gives place to a small dextro-rotation. The isomers, unlike ergosterol, have no antirachitic properties. Irradiated esters of ergosterol, with one or two exceptions, are physiologically inactive, but they acquire great activity after hydrolysis. The methyl ether of ergosterol is not activated by irradiation, and reduction of the irradiation products of ergosterol with metallic sodium destroys the antirachitic activity.

[1] Askew et al., *Proc. Roy. Soc.*, 1930, [B], **107**, 76, 91; Windaus, *ibid.*, 1931, [B] **108**, 568.

6. *Lumisterol*

This photoisomer of ergosterol yields methyl isopropyl acetaldehyde on ozonisation and it is therefore concluded that the sterol side-chain is unaffected by irradiation.[1] On dehydrogenation with selenium lumisterol is converted into 3′-methyl-1 : 2-*cyclo*pentenophenanthrene, showing that the ring system of the sterols is still intact.[2] There are three ethylenic linkages in the molecule, and also like ergosterol it yields methylbenzene tetracarboxylic acid on oxidation with nitric acid. There are several other close analogies with ergosterol, and the simplest explanation of the facts would be that lumisterol is *epi*ergosterol. This explanation, however, was found to be inadequate. As epimerization of the hydroxyl group did not account satisfactorily for the difference between lumisterol and ergosterol, attention was turned to the other points of asymmetry in the molecule and to other isomeric compounds, in particular, to pyrocalciferol and *iso*pyrocalciferol. The two pyro-compounds were obtained by the action of heat on calciferol.[3] In the transformation the tetracyclic sterol system is re-formed and the structures (III.) and (IV.) have been assigned to pyrocalciferol and *iso*pyrocalciferol respectively. Lumisterol (I.) and pyrocalciferol (II.) both yield the same dehydrolumisterol (V.). On the other hand ergosterol (III.) and *iso*pyrocalciferol (IV.) give rise to dehydroergosterol (VI.)[4]. Representing dehydrolumisterol as (V.) and dehydroergosterol as (VI.) it was concluded that the only difference between lumisterol and ergosterol was in the steric arrangement of the angle methyl group attached to carbon atom 10. The structures assigned to the four isomers and the two dehydroderivatives are given below. The structures of *epi*lumisterol (VIII.) and *epi*ergosterol (VII.) are given for comparison.

[1] Guiteras, *Annalen*, 1932, **494**, 116.
[2] Dimroth, *Ber.*, 1935, **68**, 539.
[3] Askew et al., *Proc. Roy. Soc.*, 1932, [B], 109, 488 ; Busse, *Z. physiol. Chem.*, 1933, **214**, 211.
[4] Dimroth, *Ber.*, 1936, **69**, 1123 ; Windaus and Dimroth, *ibid.*, 1937, **70**, 376.

(I) Lumisterol

(II) Pyrocalciferol

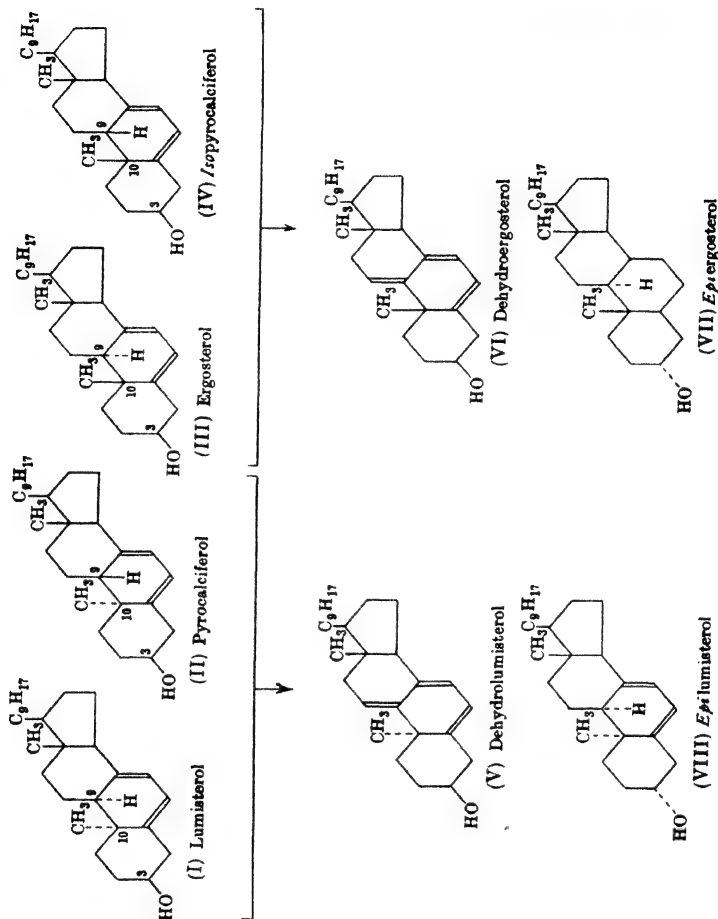
(III) Ergosterol

(IV) *iso*pyrocalciferol

(V) Dehydrolumisterol

(VI) Dehydroergosterol

(VII) *Epi*ergosterol

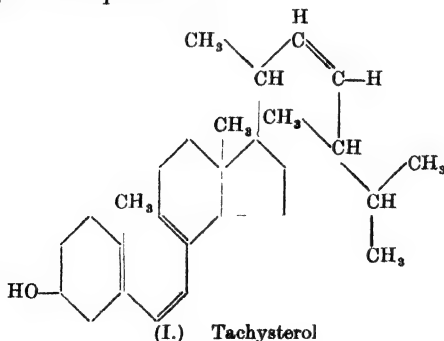
(VIII) *Epi*lumisterol

The differences in the compounds (I.) to (IV.) are explained by variations of orientation round the carbon atoms 9 and 10. The possibility that the variations were round carbon atoms 3 and 9 was found to be untenable when *epi*ergosterol (VII.) was shown to be different from either lumisterol or pyrocalciferol, and on the other hand *epi*lumisterol (VIII.) was not identical with either ergosterol or *iso*pyrocalciferol.[1] An independent connecting link has been established between the four stereoisomers (I.) to (IV.). It has been found that ergosterol, dehydroergosterol

[1] Heilbron *et al.*, *J.*, 1938, 869.

and the acetates of pyrocalciferol and dehydrolumisterol on irradiation with sunlight in the presence of eosin undergo photochemical oxidation with the formation of " bimolecular " compounds. In contrast with this behaviour lumisterol and *iso*pyrocalciferyl acetate do not form similar compounds under like conditions. In terms of the stereoisomeric structures given to these compounds the facts are taken as evidence that a positive " bimolecular " reaction, in this series of compounds indicates a *trans*-orientation of the C_{10} methyl group and the C_9 hydrogen atom, and affords additional support to the configurations given.[1]

7. *Tachysterol*

Tachysterol contains four ethylenic linkages, one of which is in the side-chain.[2] There is a conjugated system of double bonds present in the molecule as it reacts readily with citraconic anhydride.[3] It appears from these facts that the irradiation change from lumisterol to tachysterol involves the opening of the sterol ring system, presumably at ring B the seat of unsaturation in ergosterol. This view is supported by the fact that tachysterol does not yield methylbenzene tetracarboxylic acid on oxidation with nitric acid.[4] Tachysterol does not yield any formaldehyde on ozonization, so that it does not contain the methylene group present in calciferol. All these facts suggest the possible structure (I.) for tachysterol. This structure must be regarded as provisional.

(I.) Tachysterol

[1] Kennedy and Spring, *J.*, 1939, 250.

[2] Lettré, *Ann.*, 1934, **511**, 280.

[3] Windaus, v. Werder and Lüttringhaus, *Ann.*, 1932, **499**, 188.

[4] Müller, *Z. physiol. Chem.*, 1935, **233**, 223.

8. *Suprasterols I and II*

The suprasterols have not received extensive examination. The step in irradiation from calciferol to the suprasterols involves the disappearance of one ethylenic linkage and the formation of a tetracyclic system.

F.—The Vitamin E Group (The Tocopherols)

1. *Introductory*

There are three closely related compounds in this group known as α-, β-, and γ-tocopherol. They occur together in varying proportions in vegetable matter. The α- and β-compounds have been obtained from wheat-germ and other seed-germ oils, from cotton-seed oil and from green leaves. In addition the γ-compound has been isolated from cotton-seed oil and palm oil.

The presence of " vitamin E " has been found necessary in the diet of rats for normal reproduction. In female animals a deficiency of the vitamin causes sterility, and in the males it leads to degeneration of the germ cells. Prolonged deprivation of the vitamin in rats results in muscular dystrophy and degeneration of muscle fibres. Very little is known about the effects of vitamin E deficiency in other animals. Wheat-germ oil is the richest known source of the vitamins and it was from this material that concentrates of the vitamins of high physiological activity were obtained.[1] α-Tocopherol is active in rats when given in doses of 2–3 mg. When β- or γ-tocopherol is administered the quantity necessary is about 5 mg.*

2. *The Isolation of α- and β-Tocopherols*

It proved very difficult to isolate the pure substances from wheat-germ concentrates. High-vacuum distillation leads to a partial destruction of the vitamins, and such processes as chromatographic adsorption, partition of the concentrate between different solvents and esterification with acetyl and benzoyl

[1] Evans, Emerson, and Emerson, *J. Biol. Chem.*, 1936, **113**, 319.

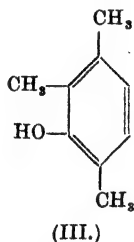
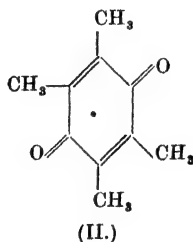
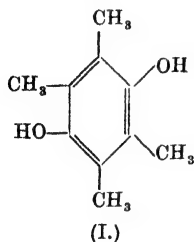
* Vitamin E activity is usually expressed as milligrams of the compound given in a single dose, required to cure sterility and produce litters in 50 per cent. of the rats used.

chlorides, although they gave preparations of high physiological activity, failed to yield crystalline products.[1] Finally, however, it was found that treatment of the vitamin concentrates with cyanic acid led to two crystalline allophanates * of the tocopherols.

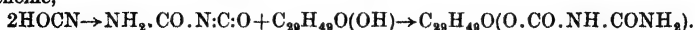
The two allophanates on separation and hydrolysis yielded α-tocopherol and β-tocopherol, both of which were pale yellow oils.

3. *The Degradation Products of α-Tocopherol*

On pyrolysis at 350° C. α-tocopherol, $C_{29}H_{50}O_2$, broke down to yield duroquinol (I.). When the heating was carried out in the presence of selenium the product was duroquinone (II.), and when hydriodic acid was used the pseudocumenol (III.) was isolated.[2]

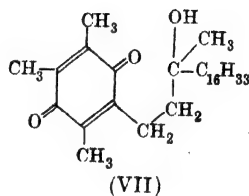
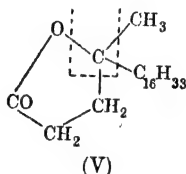
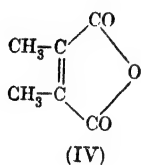
(I.) (II.) (III.)

α-Tocopherol was found to be very sensitive to oxidation, and it was by this means that valuable information about the structure of the non-benzenoid part of the cyclic system of the molecule was obtained. The action of chromic acid on the vitamin yielded dimethylmaleic anhydride (IV.) and a compound, $C_{21}H_{40}O_2$, which proved to be an optically active saturated

* Allophanic acid, NH_2—CO—NH.COOH, has not been isolated in the free state, but its salts, amides (biurets) and esters are known. Allophanates are prepared by the action of cyanic acid on alcohols. The formation of α-tocopherol allophanate may be regarded as taking place according to the scheme,

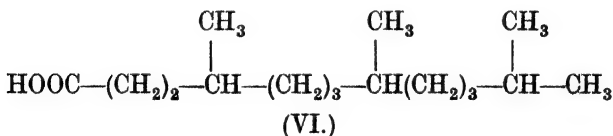
$$2HOCN \rightarrow NH_2.CO.N{:}C{:}O + C_{29}H_{49}O(OH) \rightarrow C_{29}H_{49}O(O.CO.NH.CONH_2).$$

[1] Olcott et al., *J. Biol. Chem.*, 1934, **104**, 423, 107, 471; 1935, **110**, 695; Evans, Emerson, and Emerson, *loc. cit.*; Todd, Bergel, and Work, *Biochem. J.*, 1937, **31**, 228.

[2] McArthur and Watson, *Science.*, 1937, **86**, 35; Fernholz., *J. Amer. Chem. Soc.*, 1937, **59**, 1154; John, Dietzel, and Günther, *Z. physiol. Chem.*, 1938, **252**, 208.

γ-lactone. These two products account for twenty-seven out of the total of twenty-nine carbon atoms of α-tocopherol. The free hydroxy-acid obtained from the lactone was shown to have its hydroxyl group in the tertiary form, as it could only be esterfied with difficulty, and it could not be converted into a carbonyl compound on oxidation. When α-tocopherol acetate was oxidized by chromic acid two aliphatic products were isolated, a ketone, $C_{18}H_{36}O$, and an acid, $C_{16}H_{32}O_2$. These substances were obviously related to the lactone, and to explain how they could arise by degradation of it the lactone was formulated as (V.). The $C_{16}H_{33}$ side-chain accounts for the acid, and the grouping $>C<\begin{matrix}CH_3\\C_{16}H_{33}\end{matrix}$ for the ketone.

(IV) (V) (VII)

The acid, $C_{16}H_{32}O_2$, was examined for C—CH_3 groups with positive results, and it was concluded that the chain was made up of isoprene units. In accordance with this idea the structure (VI.) was proposed for the acid : [1]

$$HOOC—(CH_2)_2—\underset{|}{\overset{CH_3}{CH}}—(CH_2)_3—\overset{CH_3}{CH}(CH_2)_3—\overset{CH_3}{CH}—CH_3$$

(VI.)

When α-tocopherol was oxidized by the comparatively mild action of gold trichloride, ferric chloride or silver nitrate a quinone containing a tertiary hydroxyl group and all the carbon atoms of α-tocopherol was isolated. The quinone has been given the structure (VII.).[2]

[1] Fernholz, *J. Amer. Chem. Soc.*, 1938, **60**, 700.
[2] John et al., *Z. physiol. Chem.*, 1938, **252**, 222; *Naturwiss.*, 1938, **26**, 366; Karrer et al., *Helv. Chim. Acta*, 1938, **21**, 939; 1940, **23**, 455.

4. *The Structure of α-Tocopherol*

The evidence given in the preceding section points to a chroman structure for the cyclic part of the tocopherol molecule. For a time it was thought that a coumaran arrangement was possible, as some of the experimental results could be equally well interpreted on the basis of such a structure for the vitamin.[1] The production of the quinone (VII.), containing a tertiary hydroxyl group, from a coumaran (VIII.) is, however, improbable, as the compound normally to be expected would be a secondary alcohol (IX.).

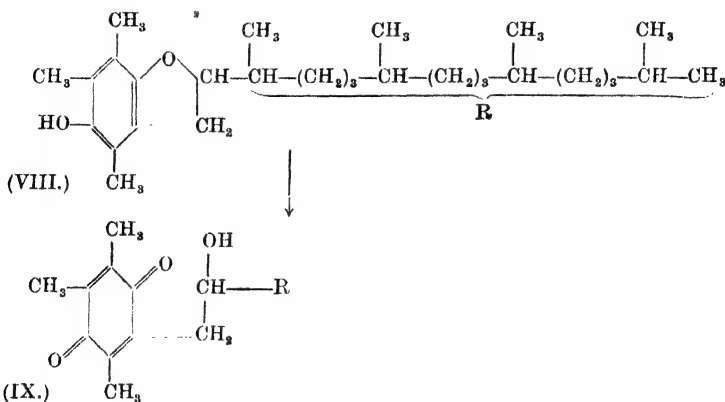
CH_3, CH_3—, HO—, O, CH_3 (ring substituents)

$CH—CH(CH_3)—(CH_2)_3—CH(CH_3)—(CH_2)_3—CH(CH_3)—(CH_2)_3—CH(CH_3)—CH_3$ (side chain = R), CH_2

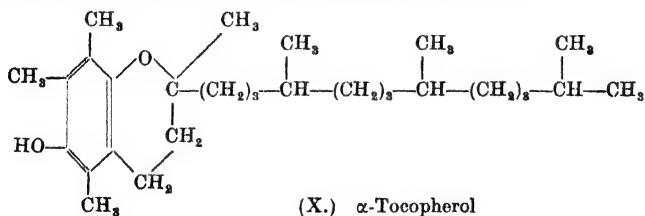
(VIII.)

↓

CH_3, CH_3—, O, O, CH_3 (quinone ring); OH, CH——R, CH_2

(IX.)

Consequently α-tocopherol was formulated as (X.):

CH_3, CH_3—, HO—, CH_3 (ring substituents), O

$C(CH_3)—(CH_2)_3—CH(CH_3)—(CH_2)_3—CH(CH_3)—(CH_2)_3—CH(CH_3)—CH_3$, CH_2, CH_2

(X.) α-Tocopherol

5. *The Synthesis of α-Tocopherol*

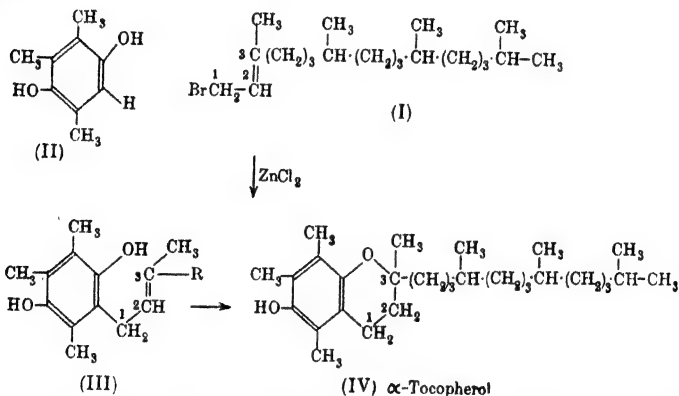
The first synthesis of α-tocopherol was accomplished by condensing phytyl bromide (I.) and pseudocumoquinol (II.) by means of zinc chloride. This reaction may be regarded as

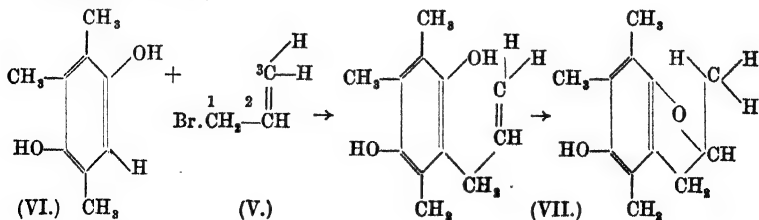
[1] Karrer et al., *ibid.*, 1938, **21**, 309, 820.

taking place in steps, the first product being the allylic phenol (III.), which then, by addition of the hydroxyl group to the ethylene linkage in accordance with the Markownikoff rule,* is converted into racemic α-tocopherol. The racemate was resolved by means of *d*-bromocamphorsulphonic acid and α-tocopherol (IV.) identical with the natural vitamin isolated.[1] The vitamin has also been obtained by similar condensations in which phytol and phytadiene were employed instead of phytyl bromide.[2]

(II) (I)

$ZnCl_2$

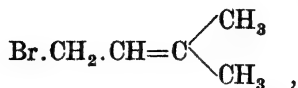
(III) (IV) α-Tocopherol

It has been shown by an extensive series of experiments that in these condensations between phenols and allyl compounds the Markownikoff rule is fully obeyed. Thus if allyl bromide, $Br{-}\overset{1}{C}H_2{-}\overset{2}{C}H{=}\overset{3}{C}\langle^{H}_{H}$ (V.), where the two groups attached to carbon atom 3 (structure V.) are hydrogen atoms, is condensed with pseudocumoquinol (VI.), the product is a coumaran (VII.).

(VI.) (V.) (VII.)

* See Vol. I., p. 179.

[1] Karrer et al., *Helv. Chim. Acta*, 1938, **21**, 520, 820.

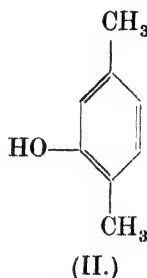
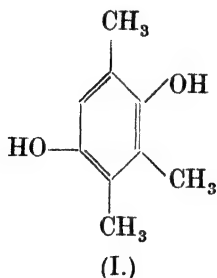
[2] Bergel, Jacob, Todd, and Work, *Nature*, 1938, **142**, 36; Smith, Ungnade, and Prichard, *Science*, 1938, **88**, 37.

On the other hand, 3 : 3-dimethylallyl bromide,

$$Br.CH_2.CH{=}C\begin{matrix}\diagup CH_3\\ \diagdown CH_3\end{matrix},$$

behaves in the same way as phytyl bromide and yields a chroman.[1]

6. *The Structures of β- and γ-Tocopherols*

β- and γ-Tocopherols are isomers with the molecular formula $C_{28}H_{48}O_2$. Pyrolysis of β-tocopherol yielded trimethylquinol (I.), and the action of hydriodic acid produced *p*-xylenol (II.).[2]

(I.) (II.)

When γ-tocopherol was decomposed by heat it also yielded trimethylquinol. Oxidation of both β- and γ-tocopherol with chromic acid gave rise to a γ-lactone, identical with that obtained from α-tocopherol.[3] These facts point to β- and γ-tocopherol, each having two methyl groups in the aromatic nucleus, with the remainders of the molecules the same as in α-tocopherol. These conclusions are supported by the syntheses of the two tocopherols from the appropriate xyloquinols and phytol or phytyl bromide, *p*-xyloquinol (III.) yielding β-tocopherol (IV.), and *o*-xyloquinol (V.) giving rise to γ-tocopherol (VI.).[4]

[1] Smith et al., *J. Amer. Chem. Soc.*, 1936, **58**, 304, 629; 1939, **61**, 2424, 2615, 3079; 1940, **62**, 142, 458, 1863; *J. Org. Chem.*, 1939, **4**, 298 *et seq.*

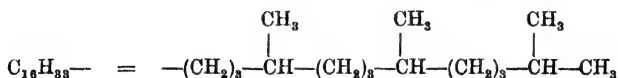
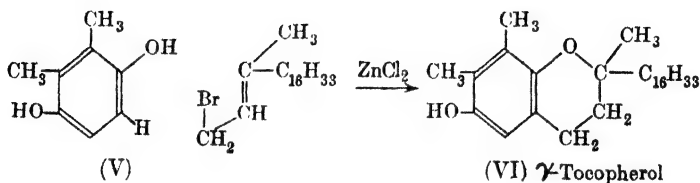
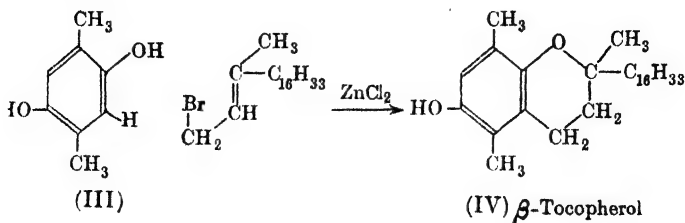
[2] John et al., *Z. physiol. Chem.*, 1937, **250**, 11; 1938, **252**, 208.

[3] Emerson, *J. Amer. Chem. Soc.*, 1938, **60**, 1741.

[4] Bergel et al., *J.*, 1938, 1382; *Nature*, 1938, **142**, 36; Jacob et al., *J.*, 1939, 542; Karrer et al., *Helv. Chim. Acta*, 1938, **21**, 520, 820, 1234; 1939, **22**, 260, 661, 1139; Smith and Ungnade, *J. Org. Chem.*, 1939, **4**, 298.

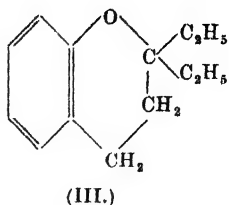
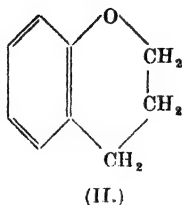
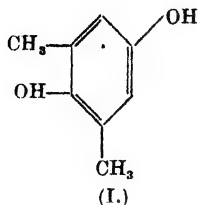
(III) + $Br-CH_2-CH=C(CH_3)-C_{16}H_{33}$ $\xrightarrow{ZnCl_2}$ (IV) β-Tocopherol

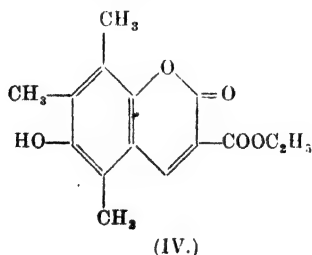
(V) + $Br-CH_2-CH=C(CH_3)-C_{16}H_{33}$ $\xrightarrow{ZnCl_2}$ (VI) γ-Tocopherol

$$C_{16}H_{33}- \; = \; -(CH_2)_3-CH(CH_3)-(CH_2)_3-CH(CH_3)-(CH_2)_3-CH(CH_3)-CH_3$$

7. *Some Other Compounds showing Vitamin E Activity*

The tocopherol derived from *m*-xylenol (I.) has a physiological activity approximately equal to that of natural β-tocopherol. Esterification of the tocopherols in some instances does not affect their activity, and in at least one case, that of the acetate of α-tocopherol, the activity is enhanced. There is a fall in activity from α-tocopherol to the β- or γ-compounds, and when the methyl groups of the aromatic nucleus are still further reduced in number, as in the tocopherol of toluquinol, physiological activity cannot be detected in doses up to 50 mg. Similarly activity is adversely affected by the replacement of methyl by ethyl groups. Shortening of the phytyl side-chain also seems to destroy activity, and the lack of even one isoprene unit in the side-chain leads to inactivity at 20 mg. doses. On the other hand some quite simple chromans have been found with vitamin E activity. Thus chroman (II.) itself, and its 2 : 2-diethyl derivative (III.) gave positive results.[1]

[1] Evans et al., *J. Org. Chem.*, 1939, **4**, 376; Jacob, Sutcliffe, and Todd, *J.* 1940, 327; Karrer and Fitzsche, *Helv. Chim. Acta*, 1938, **21**, 1622; 1939, **22**,

(I.) (II.) (III.)

A number of coumarins have been examined and only one, 6 - hydroxy - 3 - carboethoxy - 5 : 7 : 8 - trimethylcoumarin (IV.) showed activity. Other coumarins with the same substituents in the benzene ring, however, showed no activity. Turning to compounds containing a five-membered heterocyclic ring, coumaran had no activity but a number of the methyl substituted compounds had some vitamin E effect. Quinones do not appear to have any activity, but some quinols have given positive results.[1] In all over forty compounds have vitamin E activity, and it is remarkable for such a variety of substances to have specific vitamin potency.

(IV.)

G.—The Vitamin K Group

1. *Introductory*

There are two naturally occurring vitamins known. The compound isolated from alfalfa has been named vitamin K_1, or α-phylloquinone, and the physiologically less potent substance from fish meal, vitamin K_2.

A deficiency of vitamin leads to a falling off in the clotting power of blood and to subcutaneous intramuscular hæmorrhages

[1] v. Werder, Moll, and Jung, *Z. physiol. Chem.*, 1938, **254**, 39; 1939, **257**, 129.

and anæmia in chickens. The vitamins K are widely distributed in nature. Vitamin K_1 is present in relatively high concentration in the green leaves of vegetables, and to a lesser extent in the tissues of such materials as tomatoes and cereals. From animal sources hogs' liver fat and fish meal proved to be good sources of vitamin K_2.[1] The vitamins are fat-soluble, and are comparatively stable to heat. They are, however, very sensitive to light and alkali.

The preparation of the pure vitamins proved to be both difficult and laborious. Chemical methods were ineffective owing to the instability of the two compounds, and to the fact that derivatives could not be isolated in a crystalline form. In attempts to concentrate vitamin K_1 a good solvent like acetone removed large amounts of other materials as well, and made separation by vacuum distillation extremely difficult. When chromatographic adsorption was made use of to concentrate the crude extracts many of the usual adsorbents decomposed the vitamins giving rise to serious losses.

In the isolation of pure vitamin K_1 ground and dried alfalfa was subjected to percolation by a large quantity of petroleum ether. This extract was concentrated to about one-quarter of the original bulk and passed through a column of decalso, a synthetic zeolite to which the vitamins are stable. The decalso adsorption was repeated with solutions of the active fractions obtained, and the most potent fraction adsorbed twice on permutite. A final adsorption on activated charcoal yielded the pure vitamin. Molecular distillation has also been pressed into service in conjunction with chromatographic adsorption. Vitamin K_1 is a pale yellow oil.[2] The isolation of vitamin K_2 from putrefied fish meal gave the best results. It was found that bacterial putrefaction of the fish-meal gave rise to comparatively large amounts of the vitamin. A preliminary extraction of the meal with *iso*propyl ether eliminated lipoids, and the subsequent adsorption treatment of the petroleum ether

[1] Dain, *Nature*, 1935, **135**, 652; *Biochem. J.*, 1935, 29, 1273; Almquist and Stokstad, *Nature*, 1935, **136**, 31; *J. Biol. Chem.*, 1935, **111**, 105.

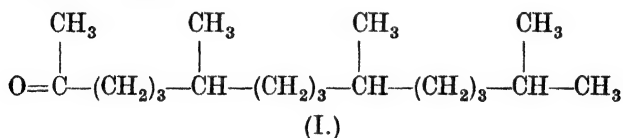
[2] Almquist, *J. Biol. Chem.*, 1937, **120**, 635; Thayer et al., *Science*, 1938, **88**, 243; Dain et al., *Helv. Chim. Acta*, 1939, **22**, 310; Karrer, *ibid.*, 1146; Almquist and Klose, *J. Amer. Chem. Soc.*, 1939, **61**, 745; Binkley et al., *J. Biol. Chem.*, 1939, **130**, 219; Karrer and Geiger, *Helv. Chim. Acta*, 1939, **22**, **945**.

extract was similar to that employed in the isolation of vitamin K_1. The vitamin was obtained as pale yellow microcrystalline plates melting at 52–53·5° C. after repeated crystallizations from different solvents.[1]

2. *The Structure of Vitamin K_1 (α-Phylloquinone)*

Vitamin K_1 has the molecular formula $C_{31}H_{46}O_2$. From its colour changes, absorption spectrum and sensitiveness to light and alkali the presence of a quinone structure in the vitamin molecule was suspected. On catalytic hydrogenation the vitamin absorbed four molecules of hydrogen. A naphthaquinone nucleus would account for three molecules of hydrogen and possibly the fourth molecule was taken up by an ethylenic linkage. Acetylation of the vitamin under reducing conditions led to the diacetate of dihydrovitamin K_1, and ozonization of this compound yielded a ketone with the molecular formula $C_{18}H_{36}O$. It was thought probable that this ketone (I.) was derived from a phytyl side-chain in the vitamin molecule, and this was shown to be correct by a comparison of the semicarbazone of the ketone with that of the ketone obtained by the oxidation of phytol.[2]

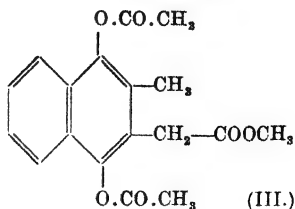
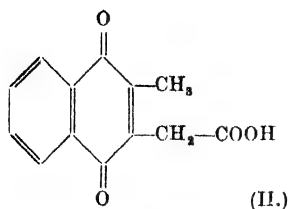
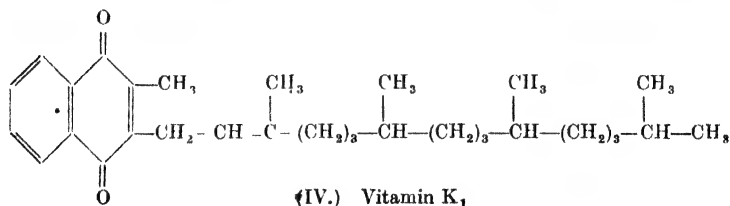
$$O{=}\underset{}{\overset{CH_3}{\overset{|}{C}}}{-}(CH_2)_3{-}\overset{CH_3}{\overset{|}{CH}}{-}(CH_2)_3{-}\overset{CH_3}{\overset{|}{CH}}{-}(CH_2)_3{-}\overset{CH_3}{\overset{|}{CH}}{-}CH_3$$

(I.)

The presence of a naphthaquinone structure in the molecule was proved by the production of phthalic acid and 2-methyl-1 : 4-naphthaquinone-3-acetic acid (II.) from the vitamin by chromic acid oxidation. When the diacetate of dihydrovitamin K_1 was oxidized with chromic acid a diacetate acid, $C_{17}H_{16}O_6$, was produced. This acid was esterified by means of diazomethane and found to be identical with a synthetic specimen of the methyl ester of 1 : 4-diacetoxy-2-methylnaphthalene-3-acetic acid (III).[3]

[1] McKee et al., *J. Biol. Chem.*, 1939, **131**, 327.

[2] Binkley et al., *J. Amer. Chem. Soc.*, 1939, **61**, 1612, 2558, 2563.

[3] Binkley et al., *loc. cit.*

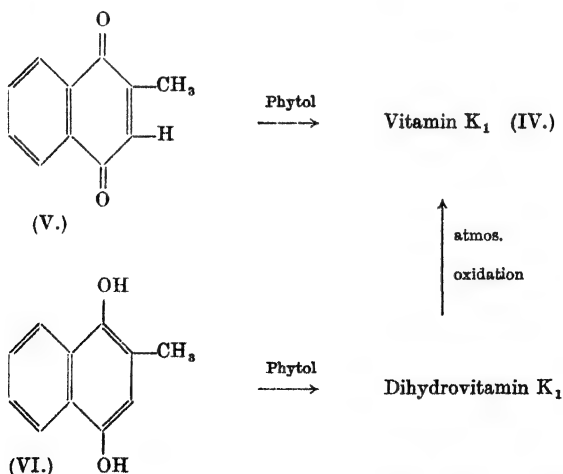
(II.) (III.)

Piecing the phytyl and quinone parts together leads to the structure 2-methyl-3-phytylnaphthaquinone (IV.) for vitamin K_1.

(IV.) Vitamin K_1

3. *The Synthesis of Vitamin K_1*

The vitamin has been synthesized both by direct condensation of phytol with 2-methyl-1 : 4-naphthaquinone (V.) and indirectly from phytol or phytyl bromide and 2-methyl-1 : 4-naphthahydroquinone (VI.) followed by atmospheric oxidation.[1]

(V.) —Phytol→ Vitamin K_1 (IV.)

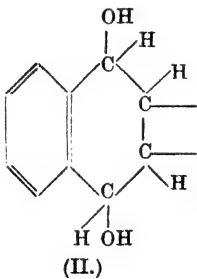
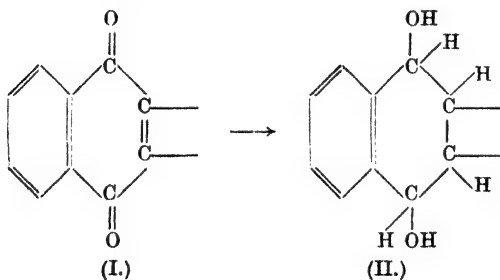
atmos. oxidation

(VI.) —Phytol→ Dihydrovitamin K_1

[1] Almquist and Klose, *J. Amer. Chem. Soc.*, 1939, **61**, 2557; Fieser et al., *ibid.*, 2559; Binkley et al., *ibid.*, 2558.

4. *The Structure of Vitamin* K_2

Vitamin K_2 has the molecular formula $C_{41}H_{56}O_2$. Its absorption spectrum resembles that of vitamin K_1, and like K_1 it yields a colourless reduction product, which readily reverts to a yellow compound on atmospheric oxidation.[1] Vitamin K_2 is sensitive to light and alkali. With these striking resemblances to vitamin K_1 it was concluded that it also was a 1 : 4-quinone.

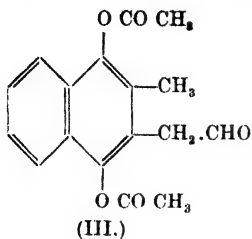
Vitamin K_2 on catalytic hydrogenation absorbed nine molecules of hydrogen, and on reductive acetylation yielded the diacetate of dihydrovitamin K_2, which was capable of absorbing eight molecules of hydrogen and six molecules of bromine. The bromine absorption indicated the presence of six ethylenic linkages in the molecule. The fact that the vitamin is capable of taking up a total of nine molecules of hydrogen is in agreement with the conclusion that the molecule contains the 1 : 4-naphthaquinone structure (I.), three of the hydrogen molecules giving rise to a tetrahydronaphthahydroquinone grouping (II.) and the remaining six molecules entering the side-chain or chains.[2]

(I.) → (II.)

Oxidation of the vitamin with potassium permanganate yielded phthalic acid, and in acetic acid the action of ozone followed by treatment with zinc in ether yielded 1 : 4-diacetoxy-2-methylnaphthalene-3-acetaldehyde (III.). These facts show unmistakably that vitamin K_2 is a 2-methyl-1 : 4-naphthaquinone. Ozonization also yielded lævulinic aldehyde (IV.) and acetone.

[1] McKee et al., *J. Amer. Chem. Soc.*, 1939, **61**, 1295.
[2] McKee et al., *J. Amer. Chem. Soc.*, 1939, **131**, 327.

$O\,CO\,CH_3$ / —CH_3 / —$CH_2.CHO$ / $O\,CO\,CH_3$

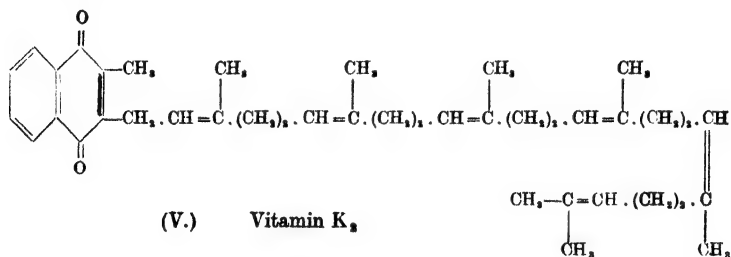
(III.)

CH_3—CO—CH_2—CH_2.CHO

(IV.)

On the assumption that five molecular proportions of lævulinic aldehyde would originate from one of vitamin a 93 per cent. yield was obtained. Farnesol ozonized under similar conditions gave a 75 per cent. yield of the aldehyde. The fragments from one of the naphthaquinone, one of acetone and five of lævulinic aldehyde account for the forty-one carbon atoms of the vitamin molecule, and the simplest arrangement of the side-chain at position 3 of the quinone system is a head to tail attachment of six isoprene units with an ethylenic linkage at each carbon atom bearing a methyl group. This leads to structure (V.) for vitamin K_2.[1]

O / O / —CH_3

—CH_2.CH=C(CH_3).$(CH_2)_2$.CH=C(CH_3).$(CH_2)_2$.CH=C(CH_3).$(CH_2)_2$.CH=C(CH_3).$(CH_2)_2$.CH=C(CH_3).$(CH_2)_2$.C(CH_3)=CH.$(CH_2)_2$.CH=C(CH_3)—CH_3

(V.) Vitamin K_2

H.—Conclusion

On comparing the structures given to the different vitamins two features stand out. Firstly, the wide variety of structures found for the compounds, which may be illustrated by reference to vitamin B_1 and ascorbic acid or the vitamins D. Even in the sub-group of vitamin B_2 two such different compounds as the yellow pigment *d*-riboflavin and the aliphatic amide pantothenic acid are found.

[1] Binkley et al., *J. Biol. Chem.*, 1940, **133**, 721.

Secondly, the structural relationships which exist amongst the vitamins. Connections like the presence of the pyrimidine grouping in both vitamin B_1 and *d*-riboflavin and the very close relationship between adermin and nicotinic acid strike the eye; and the presence of the phytyl skeleton, or to think in terms of a smaller unit, the isoprene grouping, in vitamins A, E, and K is a tantalizing fact which opens up still further the region of "isoprene" speculation. This same grouping of head to tail isoprene units may be traced in vitamin D_3. Although these four groups of vitamins have been brought together in this way, the unique feature is the still closer chemical relationship existing between the tocopherols and the K vitamins. The knowledge gained during work on the tocopherols was of great value in the study of the vitamins K, as the syntheses of both have several features in common. Phytol or phytyl bromide may be employed in each synthesis in conjunction with a quinol. The tocopherols are formed with great ease from these reagents, and it is not surprising that the naphthaquinols also yield tocopherols in considerable quantities when these reagents are used. Finally, one more parallel between the vitamins of the E and K groups may be mentioned. Specific physiological activity is not limited to the vitamins themselves. There is a wide range of compounds related to the tocopherols which have vitamin E potency, and similarly many naphthaquinones show anti-hæmorrhagic activity.

CHAPTER III

THE HORMONES

A.—Introductory

Certain organs in the higher animals have the power of forming substances, which can be sent into the blood-stream to control or excite some other part of the system. Because of their exciting action, Starling, one of the pioneers in this branch of physiology, suggested that these chemical messengers should be called hormones. This name has been generally adopted and the definition widened to include certain plant products. It had been known for many years that the effects of thyroid deficiency in man could be rectified by administration of the gland in the form of powder or extract, and that there was a connection between iodine and the normal working of the organ. Similarly *diabetes mellitus* was known to be connected with the failure of some part of the pancreas. With the exception of adrenaline, which was studied in the early years of the present century, our knowledge of the chemical constitutions of the hormones is of comparatively recent date. The active iodine-containing glandular substance known as thyroxine was synthesized by Harington and Barger [1] in 1927. In more recent years steady advances have been recorded in the chemistry of the sex hormones, and gradually the structural relationships of these compounds among themselves and their kinship with such substances as cholesterol and the bile acids, are becoming clearer. Work on the hormones is difficult owing to their instability and to the extremely small quantities present in the organs. Their great physiological activity, however, invests them with an importance out of all proportion to their quantitative occurrence. The hormones being mainly the products of glands, it might be thought that they would be enzymic in character; for enzymes are active agents in many external secretions like those of the salivary, gastric and intestinal glands. The hormones, however,

[1] *Biochem. J.*, **21**, 169 (1927).

are not enzymes. They are much simpler in chemical structure, and are not affected physically and chemically in the same way as the enzymes.

B.—The Thyroid Hormone. Thyroxine

1. *General*

Bodily disorders resulting from improper functioning of the thyroid gland fall into two main groups; on the one hand, those due to its over-activity, and on the other hand, those which are the outcome of subnormal activity or development of the gland. These latter troubles are curable or the symptoms can be allayed by administration of thyroid preparations. It became then a matter of the first importance to isolate and identify the physiologically active compound of the gland. Baumann [1] in 1895 discovered iodine in the gland. Kendall [2] in 1915 obtained two iodine-containing solids, and subsequently in 1919 isolated the substance, which he named "thyroxin," in a pure crystalline condition. The chemistry of thyroxine has been studied by various workers, notably Harington, and its synthesis was finally accomplished by Harington and Barger.[3]

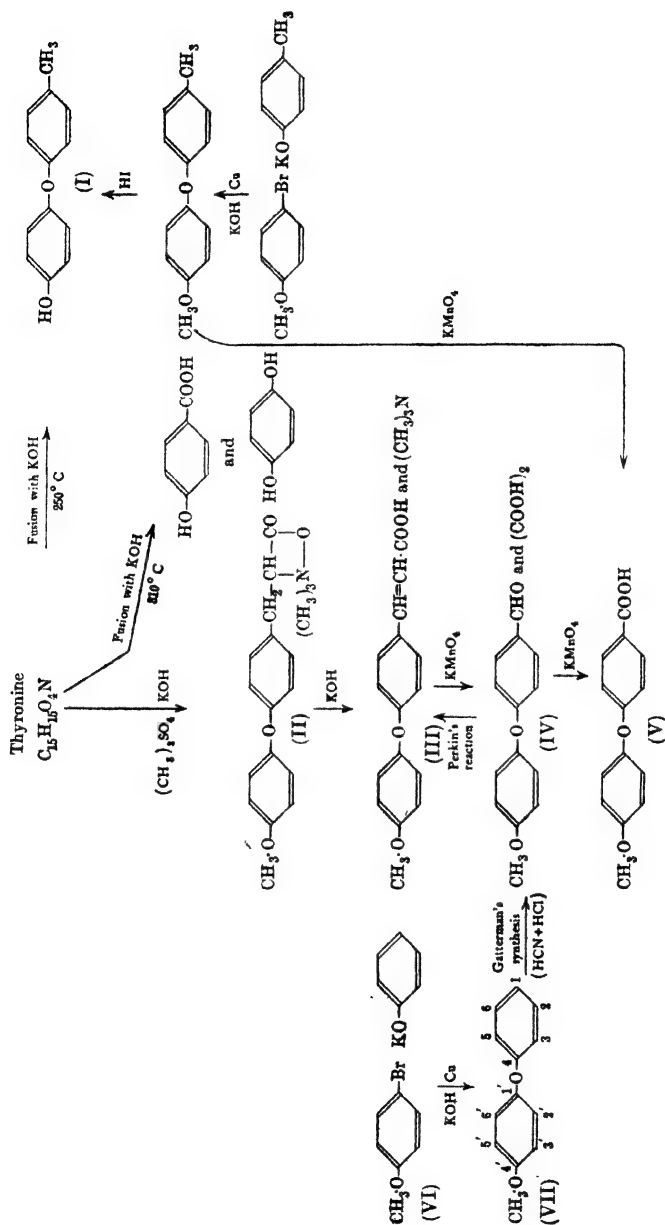
2. *The Constitution of Thyroxine*

The proof of the structure of the thyroxine molecule may be divided into four parts, (*a*) determination of the structure of thyronine (desiodo-thyroxine), (*b*) the properties of thyroxine, and certain theoretical considerations, (*c*) the investigation of the structures of other thyroxine derivatives, (*d*) the synthesis of thyroxine.

(*a*) *The determination of the structure of thyronine.*—This establishes the principal parts of the thyroxine constitution. Thyroxine has been given the molecular formula, $C_{15}H_{11}O_4NI_4$, and thyronine, $C_{15}H_{15}O_4N$. Thyronine is obtained in almost theoretical yield by shaking a potassium hydroxide solution of thyroxine in an atmosphere of hydrogen and using palladium

[1] *Z. physiol. Chem.* (1895–96), **21**, 319.
[2] *J. Biol. Chem.*, 1915, **20**, 501; 1919, **39**, 125.
[3] Harington, *Biochem. J.*, 1926, **20**, 293, 300; 1928, **22**, 1429, 1436; Harington and Barger, *ibid.*, 1927, **21**, 169.

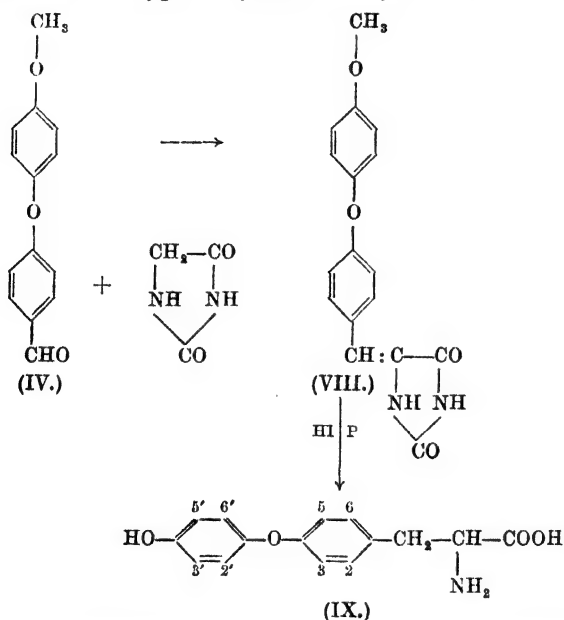
hydroxide precipitated on calcium carbonate as a catalyst. Iodine is quantitatively split off as potassium iodide, and four atomic proportions of hydrogen taken up. It may be assumed then that thyronine is thyroxine with four iodine atoms replaced by hydrogen atoms. Thyronine is amphoteric, it gives the Millon reaction for aromatic substances containing a hydroxyl group attached to the benzene nucleus, a positive reaction by the ninhydrin test for an amino acid with a free carboxyl and a free amino group. The total nitrogen of thyronine is liberated by the action of nitrous acid. These facts point to the substance being an α-amino-acid containing a phenolic group. Three of the four oxygen atoms are thus accounted for. The fourth oxygen atom is chemically inert and is ethereal in character. When thyronine is fused with potassium hydroxide at 310° C. in an atmosphere of hydrogen, it yields *p*-hydroxybenzoic acid, hydroquinone, oxalic acid and ammonia; at 250° C. the principal product is 4-(4′-hydroxyphenoxy)-toluene (I.), along with some oxalic acid and ammonia. On exhaustive methylation thyronine yields a betaine (II.) from which trimethylamine can be split off leaving an unsaturated acid (III.) of molecular formula, $C_{16}H_{14}O_4$, and oxidation of this acid yields an aldehyde (IV.), $C_{14}H_{12}O_3$, and oxalic acid. The formation of oxalic acid here, and during the potash fusions, points to the presence of a three-carbon side-chain in the molecule. The aldehyde, $C_{14}H_{12}O_3$, on oxidation, yields an acid, $C_{14}H_{12}O_4$ (V.). The molecular structures of the compounds (I.), (III.), (IV.), and (V.) were established by their syntheses. The following scheme shows the structures and syntheses of the thyronine derivatives.

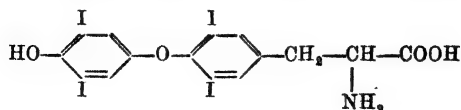
Thyronine
$C_{15}H_{15}O_4N$
Fusion with KOH 250° C
Fusion with KOH 310° C
$(CH_3)_2SO_4$ KOH
HI
KOH Cu
and
KOH
KMnO₄
Perkin's reaction
Gatterman's synthesis (HCN+HCl)
(I)
(II)
(III)
(IV)
(V)
(VI)
(VII)
CH=CH·COOH and $(CH_3)_3N$
CHO and $(COOH)_2$

Thyronine has been synthesized from *p*-bromoanisol (VI.) and phenol.[1] When these two compounds are heated with potassium hydroxide and copper bronze, 4′-methoxyphenoxy benzene (VII.) is produced. This compound can be converted into 4-(4′-methoxyphenoxy)-benzaldehyde (IV.) by Gatterman's synthesis. The aldehyde can be condensed with hydantoin with the formation of 4-(4′-methoxyphenoxy)-benzylhydantoin (VIII.). This hydantoin derivative when boiled with hydriodic acid and red phosphorus is simultaneously reduced, hydrolysed and demethylated, yielding thyronine (IX.). The steps in the synthesis from 4-(4′-methoxyphenoxy)-benzaldehyde are shown below.

CH_3—O—C_6H_4—O—C_6H_4—CHO (IV.) + CH_2—CO / NH NH / CO ⟶ CH_3—O—C_6H_4—O—C_6H_4—CH : C——CO / NH NH / CO (VIII.)

HI | P ↓

HO—C_6H_4—O—C_6H_4—CH_2—CH—COOH (positions 5′ 6′ 3′ 2′; 5 6 3 2)
                                        |
                                       NH_2

(IX.)

(*b*) *The properties of thyroxine and certain theoretical considerations.*—Harington gave thyroxine the structure,

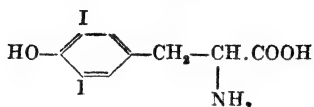
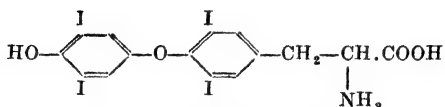
HO—$C_6H_2I_2$—O—$C_6H_2I_2$—CH_2—CH—COOH
                                        |
                                       NH_2

Thyroxine, when fused with potash at a high temperature, gave products which showed pyrogallol reactions. From this it

[1] Harington, *Biochem. J.*, 1926, **20**, 300.

appeared that one or both benzene rings of the molecule passed into 3 : 4 : 5-trihydroxy derivatives. The colour reaction given by thyroxine with nitrous acid and ammonia is also given in general by benzene derivatives which have two iodine atoms in the ortho positions to the hydroxyl or amino group. 3 : 5-Diiodotyrosine occurs in the thyroid gland as well as thyroxine. When the two structures are compared,

I
HO—⟨ ⟩—CH$_2$—CH.COOH
I | NH$_2$

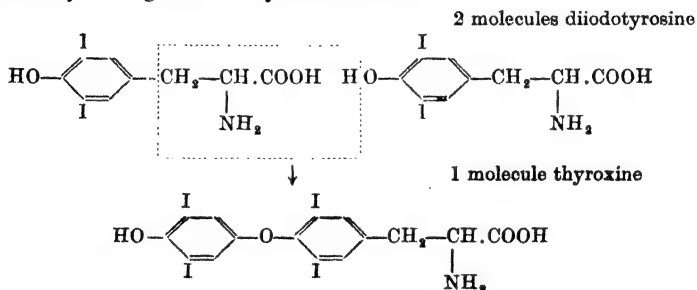
and

I I
HO—⟨ ⟩—O—⟨ ⟩—CH$_2$—CH.COOH
I I | NH$_2$

it is reasonable to think that the tyrosine derivative is the precursor of thyroxine in the gland, two molecules of diiodotyrosine yielding one of thyroxine, thus,

2 molecules diiodotyrosine

I I
HO—⟨ ⟩—CH$_2$—CH.COOH HO—⟨ ⟩—CH$_2$—CH.COOH
I | NH$_2$ I | NH$_2$

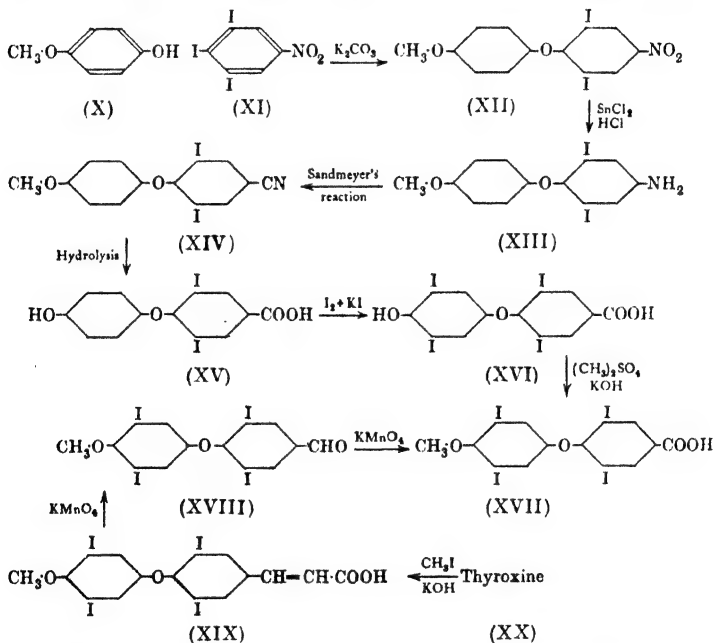
↓ 1 molecule thyroxine

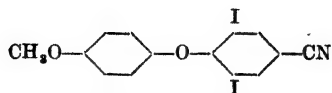
I I
HO—⟨ ⟩—O—⟨ ⟩—CH$_2$—CH.COOH
I I | NH$_2$

(*c*) *The investigation of the structures of other thyroxine derivatives.*—When thyroxine (XX.) is exhaustively methylated an unsaturated acid, $C_{16}H_{10}O_4I_4$ (XIX.), can be isolated, which on oxidation is converted into the corresponding aldehyde, $C_{14}H_8O_3I_4$ (XVIII.). On further oxidation the aldehyde yields a tetra iodo-4-(4′-methoxyphenoxy) benzoic acid (XVII.). This acid can be synthesized from 3 : 4 : 5-triiodonitrobenzene (XI.) and hydroquinone monomethyl ether (X.). Triiodonitrobenzene was originally selected as the nitro group makes the para-iodine atom labile without affecting the two meta atoms. The ether, 3 : 5 diiodo-4-(methoxyphenoxy) nitrobenzene (XII.) resulting from the condensation is reduced to the corresponding aniline

(XIII.), and from this by Sandmeyer's reaction the nitrile (XIV.) is obtained. The nitrile when boiled with a mixture of hydriodic and acetic acids undergoes demethylation and hydrolysis to the acid, 3 : 5-diiodo-4-(4′-hydroxyphenoxy) benzoic acid (XV.). The acid when dissolved in concentrated ammonia and iodinated, yields 3 : 5-diiodo-4-(3′ : 5′-diiodo-4′-hydroxyphenoxy) benzoic acid (XVI.). On methylation this acid is converted into a compound (XVII.) identical in every way with the substance obtained by the exhaustive methylation and subsequent oxidation of thyroxine. The diagram will make the different steps clearer.

CH_3O–C₆H₄–OH (X) + I₂C₆H₂(I)–NO_2 (XI) $\xrightarrow{K_2CO_3}$ CH_3O–C₆H₄–O–C₆H₂I₂–NO_2 (XII) $\xrightarrow{SnCl_2,\ HCl}$ CH_3O–C₆H₄–O–C₆H₂I₂–NH_2 (XIII) $\xrightarrow{\text{Sandmeyer's reaction}}$ CH_3O–C₆H₄–O–C₆H₂I₂–CN (XIV)

(XIV) $\xrightarrow{\text{Hydrolysis}}$ HO–C₆H₄–O–C₆H₂I₂–COOH (XV) $\xrightarrow{I_2 + KI}$ HO–C₆H₂I₂–O–C₆H₂I₂–COOH (XVI) $\xrightarrow{(CH_3)_2SO_4,\ KOH}$ CH_3O–C₆H₂I₂–O–C₆H₂I₂–COOH (XVII)

Thyroxine (XX) $\xrightarrow{CH_3I,\ KOH}$ CH_3O–C₆H₂I₂–O–C₆H₂I₂–CH=CH·COOH (XIX) $\xrightarrow{KMnO_4}$ CH_3O–C₆H₂I₂–O–C₆H₂I₂–CHO (XVIII) $\xrightarrow{KMnO_4}$ (XVII)

(*d*) *The synthesis of thyroxine.*—The preliminary steps are the same as in the synthesis of 3 : 5-diiodo-4-(3′ : 5′-diiodo-4′-methoxyphenoxy) benzoic acid (XVII., above), as far as the nitrile,

CH_3O—C₆H₄—O—C₆H₂I₂—CN

(XIV., above). The nitrile is treated with an ethereal solution of stannous chloride and hydrogen chloride, the aldehyde (I.)

formed is condensed with hippuric acid to produce the azlactone (II.), and from this an acrylic acid derivative (III.) is obtained by heating with one per cent. alcoholic sodium hydroxide. The unsaturated acid (III.), when boiled with a mixture of hydriodic acid, acetic anhydride and red phosphorus, is simultaneously demethylated, reduced to the saturated side-chain, and hydrolysed at the benzamido group to yield 3 : 5-diiodothyronine (IV.). The conversion of the diiodo compound into thyroxine is accomplished by dissolving it in strong ammonia solution and adding a solution of iodine in potassium iodide. The tetraiodo compound (V.) obtained is identical with thyroxine from natural sources. The scheme shows the structures of the different compounds.

$CH_3.O—C_6H_4—O—C_6H_2I_2—CN \xrightarrow[HCl]{SnCl_2} CH_3O—C_6H_4—O—C_6H_2I_2—CHO$

(I.)

↓ $CH_2.COOH$ | $NH.CO.C_6H_5$

$CH_3.O—C_6H_4—O—C_6H_2I_2—CH : C—CO$ (ring closed through O to) $N=C.C_6H_5$

(II.)

↓ NaOH

$CH_3O—C_6H_4—O—C_6H_2I_2—CH=C—COOH$ | $NH.CO.C_6H_5$

(III.)

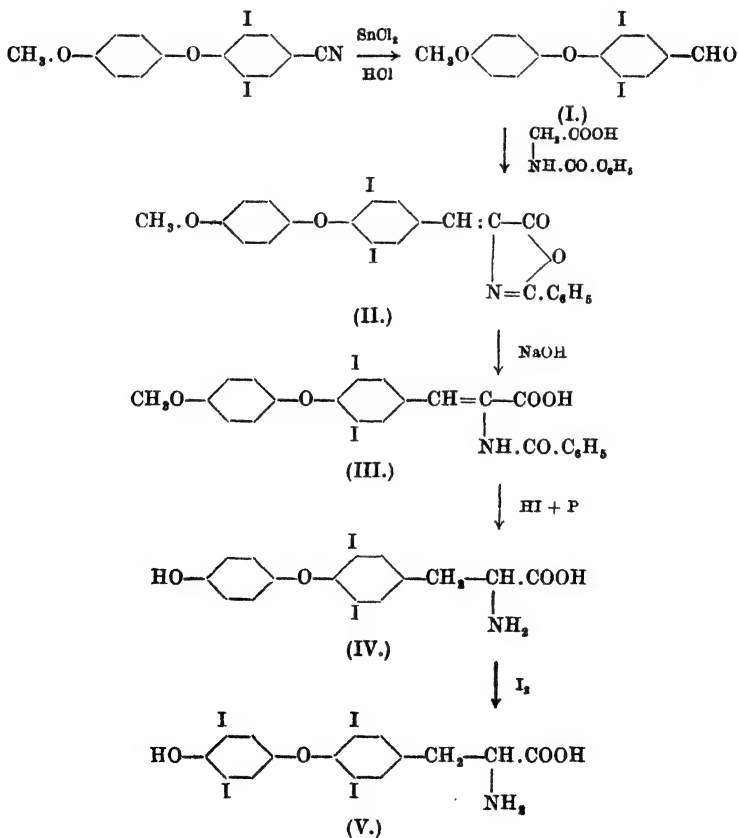
↓ HI + P

$HO—C_6H_4—O—C_6H_2I_2—CH_2—CH.COOH$ | NH_2

(IV.)

↓ I_2

$HO—C_6H_2I_2—O—C_6H_2I_2—CH_2—CH.COOH$ | NH_2

(V.)

C.—The Female Sex Hormones. Oestrone, Oestriol and Equilenin

1. *General*

In recent years the hormones which cause oestrus in female animals have been isolated and examined chemically. These hormones are secreted by the ovaries. After double ovariectomy the usual oestrual changes cease, and it has been found that the hormones extracted from ovarian tissue when injected into the animal produce the phenomena of oestrus. They may be obtained from various other sources, such as the corpus luteum, female blood and the urine of pregnancy. Allan and Doisy described their first work on ovarian hormones in 1923.[1] In 1929 Marrian isolated a pure crystalline oestrus-producing substance from human urine, and about the same time Butenandt obtained another active substance from the same source.[2] As the structures of these compounds and of the cholane substances were elucidated, it became obvious that there is a very close connection structurally between the two groups.

2. *The Constitutions of Oestrone, Oestriol and Equilenin*

Oestrone and oestriol are very closely related structurally, as oestriol by the loss of the elements of water is converted into oestrone. The two compounds are not interconvertible by any of the treatments employed in their isolation, and therefore both must be present in the original urine. Oestrone has been given the molecular formula, $C_{18}H_{22}O_2$, and oestriol, $C_{18}H_{24}O_3$. The phenolic character of oestrone was early recognized. It forms a monoacetate, a monomethyl ether, a mono-oxime and a semicarbazone, pointing to the presence of a hydroxyl and a

[1] *J. Am. Med. Ass.*, 1923, **81**, 819.
[2] Marrian, *Biochem. J.*, 1929, **23**, 1090; Butenandt, *Ber.*, 1930, **63**, 659; *Z. physiol. Chem.*, **1930**, **191**, 127, 140.

keto group. Oestriol also contains one phenolic group and in addition two secondary alcoholic groups. These two alcoholic hydroxyls are adjacent, and it is concluded that the loss of water is from them with the formation of the oestrone keto group. On catalytic hydrogenation oestrone is converted into a compound $C_{18}H_{30}$, and distillation with zinc yields an aromatic hydrocarbon, $C_{18}H_{14}$. These results indicate the presence of three double bonds in the molecule, and it is inferred that they are in the same ring. That is, one aromatic nucleus is present.[1] These conclusions are supported by measurements of molecular refraction and ultra-violet absorption spectra.[2]

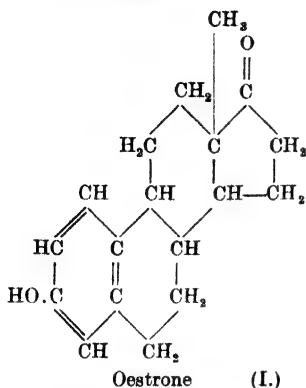
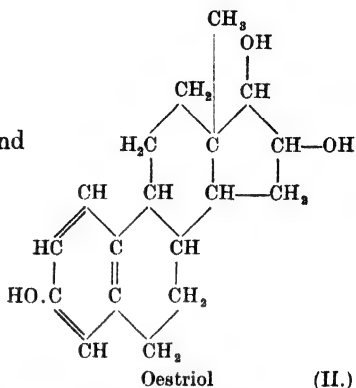
Ethylenic double bonds are absent as the product of bromination is a monobromo substituted compound. The comparative stability of oestrone to alkaline potassium permanganate and to potash fusion at a high temperature suggests the possibility of a condensed carbon ring structure similar to the anthracene or phenanthrene skeleton. If $C_{18}H_{24}$ be regarded as the molecular formula of the parent hydrocarbon, it must have a fused ring structure, one of the rings being a benzene nucleus. Some of the properties of unimolecular films of oestrone and oestriol derivatives have been investigated with interesting results. Surface pressures, the outward force on a barrier in the surface dividing the film-covered surface from a water surface, were measured by means of the apparatus of Adam and Jessop. The films were also examined for collapse, and the change in the electrical potential at the air-liquid surface recorded.[3] It was concluded that the molecular structures contained a phenanthrene, anthracene, naphthacene, chrysene or a 2 : 3-benzphenanthrene skeleton, and that the two alcoholic hydroxyls of oestriol are together on the same side of a ring, the phenolic hydroxyl being at the opposite end of the molecule. Crystallographic and X-ray examinations of oestrone and oestriol also suggested structures of the condensed ring type, and the relative positions of the hydroxyl groups were indicated.

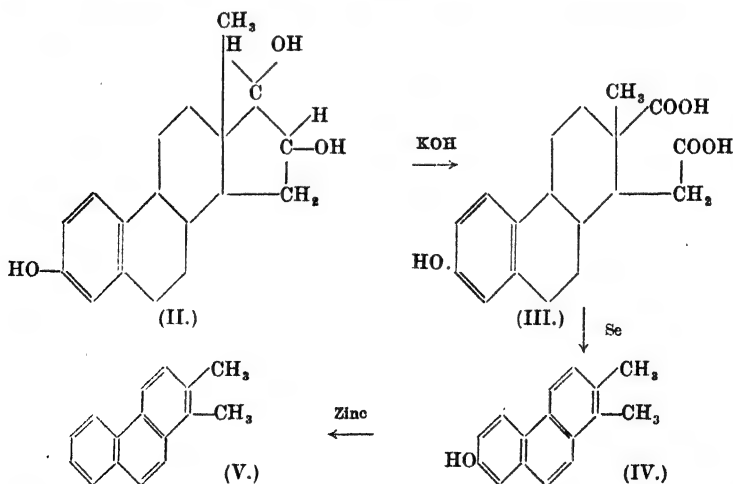
[1] Marrian and Haslewood, *Biochem. J.*, 1932, **26**, 25.

[2] Butenandt, *Angew. Chem.*, 1932, **45**, 655 ; *Nature*, 1932, **130**, 238.

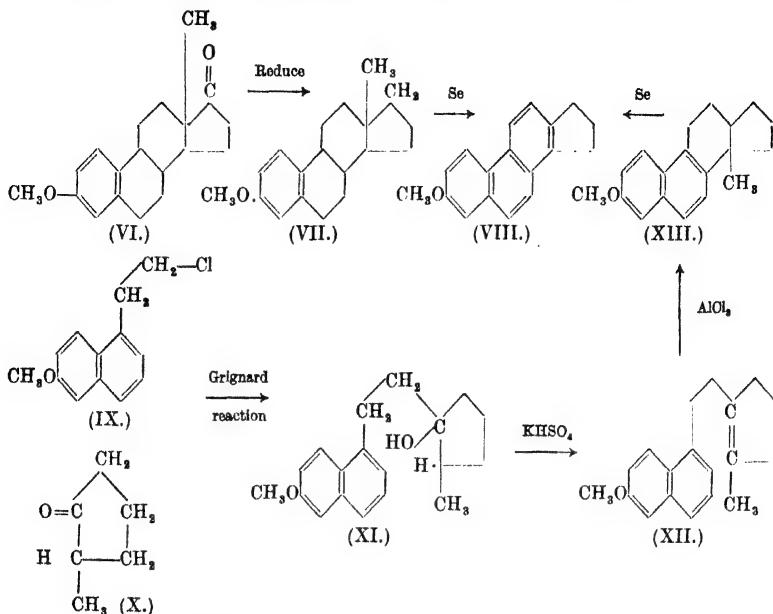
[3] Adam, Danielli et al., *Biochem. J.*, 1932, **26**, 1233 ; *J.S.C.I.*, 1932, **51**, 1075.

The two compounds, oestrone and oestriol, have been given the structures,

Oestrone (I.) and Oestriol (II.)

These structures are in agreement with the facts so far mentioned. Further evidence is also in agreement. When oestriol (II.) is fused with potash it yields a dicarboxylic acid, $C_{18}H_{22}O_5$ (III.). This acid, on dehydrogenation by means of selenium, is converted into 1 : 2-dimethyl-7-hydroxyphenanthrene (IV.) and this by the action of zinc dust passes into 1 : 2-dimethyl-phenanthrene (V.). These changes may be formulated as follows : [1]

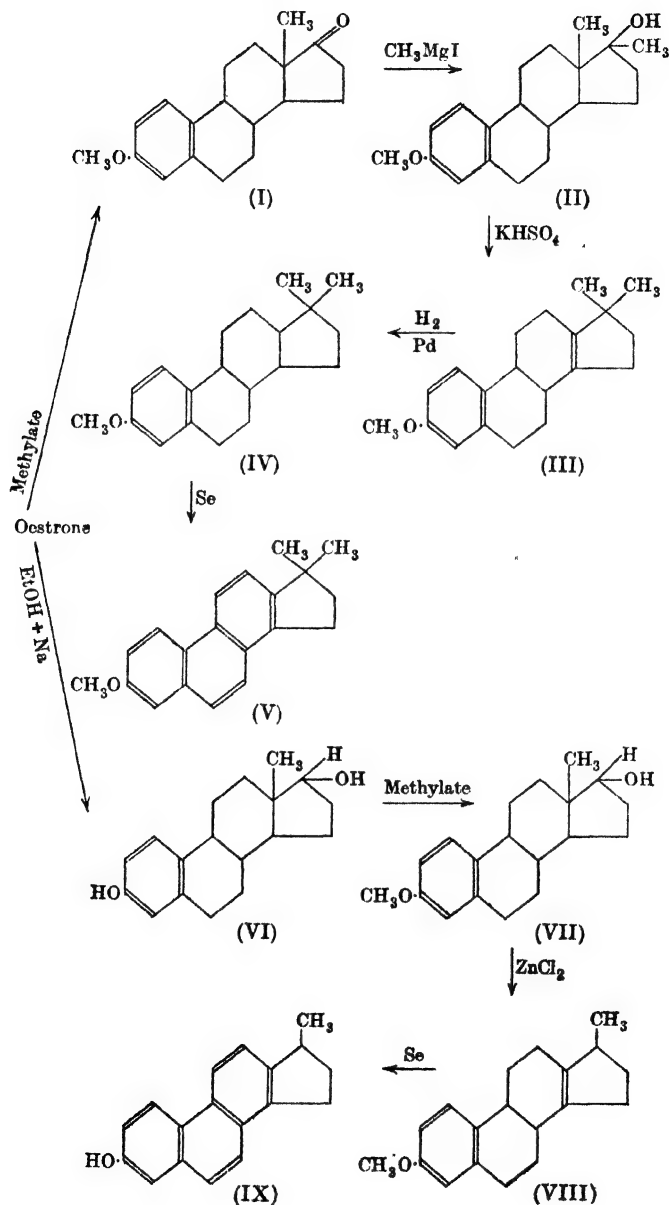
(II.) —KOH→ (III.) —Se→ (IV.) —Zinc→ (V.)

[1] Butenandt, Weidlich, and Thompson, *Chem. and Ind.*, 1933, **52**, 268; *Ber.*, 1933, **66**, [B], 601.

The positions of the two methyl groups in 1 : 2-dimethyl-7-hydroxyphenanthrene have been proved by its synthesis, and show the point of attachment of the five-membered ring in oestriol, which is suggested by the conversion of the two secondary alcoholic groups into two carboxyl groups without loss of carbon atoms. The next work demonstrates beyond doubt the skeleton of oestrone and fixes the position of the phenolic group.[2] When oestrone (I.) is methylated (VI.), reduced at the keto group and the desoxy-compound (VII.) dehydrogenated with selenium the methoxy compound (VIII.) is formed. The structure of compound (VIII.) was confirmed by its synthesis. The steps in the synthesis from β-6-methoxy-1-naphthyl ethyl chloride (IX.) are as follows: the Grignard solution of the chloride, when allowed to interact with 2-methyl*cyclo*pentanone (X.) yielded first the carbinol (XI.), and then by dehydration with potassium hydrogen sulphate, the *cyclo*pentene derivative (XII.). When the *cyclo*pentene derivative was treated with anhydrous aluminium chloride a tetracyclic methoxy compound (XIII). was formed, and this, when heated with selenium, passed into 7-methoxy-1 : 2-*cyclo*pentenophenanthrene (VIII.), which proved to be identical with the compound obtained by the degradation of oestrone. The scheme will make the steps in the degradation and synthesis clearer,

[1] Cook and Girard, *Nature*, 1934, **133**, 377; Cohen, Cook, Hewett, and Girard, *J.*, 1934, 653.

The remaining two problems,[1] the positions of the keto and the quaternary methyl groups, have been solved by further study of the degradation products of oestrone and their syntheses.

When methoxy-oestrone (I.) below, reacts with methyl magnesium iodide, the methyl carbinol (II.) is formed. On dehydration the carbinol is converted into the unsaturated compound (III.). Catalytic hydrogenation and finally selenium dehydrogenation yielded 7-methoxy-3′ : 3′-dimethyl-1 : 2-*cyclo*-pentenophenanthrene (V.). It is assumed by analogy with well-known cases that dehydration of the carbinol (II.) is accompanied by migration of the quaternary methyl group to the adjacent position in the five-membered ring. The second line of attack of the problem is also through oestrone. Oestrone, in alcoholic solution, is reduced at the keto group by sodium and a dihydroxy-oestratriene (VI.) formed. This compound is methylated and the methyl ether (VII.) dehydrated with zinc chloride. The dehydration product (VIII.) is assumed to be formed by the migration of the methyl group as in the previous case. When heated with selenium, compound (VIII.) yields 7-methoxy-3′-methyl-1 : 2-*cyclo*pentenophenanthrene (IX.).

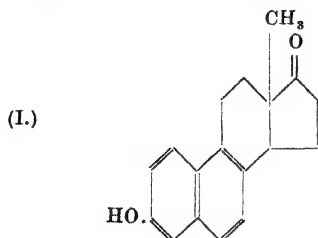
[1] Cohen, Cook and Hewett, *J.*, 1935, 445.

These two series of changes are shown diagrammatically below.

These two end-products, (V.) and (IX.), have been synthesized from β-6-methoxy-1-naphthyl ethyl bromide with 2 : 2 : 5 trimethyl- and 2 : 5-dimethyl-*cyclo*pentanone respectively by the method already given (page 104), for the synthesis of 7-methoxy-1 : 2-*cyclo*pentenophenanthrene. It is concluded that the quaternary methyl group in oestrone is in position C_{13} (sterol numbering), and migrates to the adjacent carbon atom C_{17}, the original position of the keto group, during dehydration of the carbinol ; and since oestrone is obtained from oestriol by the elimination of the elements of water, it follows that the two secondary alcoholic hydroxyls of oestriol occupy positions C_{16} and C_{17}.

The numberings of the rings and carbon atoms for the oestrins are the same as in the bile acids and sterols.

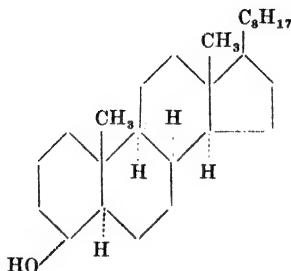
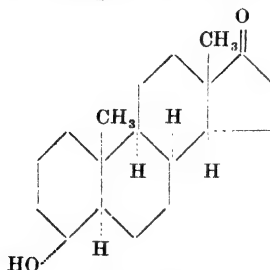
Equilenin, which is also oestrogenic, has been isolated and given the molecular formula, $C_{18}H_{18}O_2$. It is similar to oestrone in chemical properties, but differs from it in having a greater acidity and two aromatic rings in the molecule. Equilenin has been given the constitution (I.), and is therefore a natural dehydrogenation product of oestrone.

(I.)

CH_3 O HO.

D.—The Male Sex Hormone. Androsterone

This hormone controls the secondary sex characters of male animals, and is closely related structurally to oestrone. Potent extracts may be prepared from the testes of bulls, goats, etc., and from male blood and urine. The activity of an extract is measured by the comb growth test in capons. The areas or lengths of the combs of castrated birds are measured after injections and compared with the combs of control birds. A potent extract causes rapid growth of the comb, and when injections are withheld the comb becomes impoverished. Androsterone has been isolated in very small quantities and examined.

Its molecular formula is $C_{19}H_{30}O_2$. It resembles oestrone in being a hydroxy-ketone. It yields a diketone on oxidation, and from this diketone by Clemmensen's method of reduction the hydrocarbon, androstane, has been isolated.

The androsterone molecule, unlike oestrone, contains no benzene nucleus, the rings are fully saturated. It has been isolated [1] as an oxidation product of epicholestanol, one of the sterol group of compounds. Epicholestanol has been given the space formula,

and androsterone the corresponding formula,

This formula expresses the relationship of androsterone to oestrone and to the sterols.

E.—Corpus Luteum Hormone. Progesterone

The hormone of the internal secretion of the corpora lutea has been isolated from the crude semicarbazone and purified in sufficient quantity to allow its molecular formula, $C_{21}H_{30}O_2$, to be determined, and its chemical nature to be investigated. Progesterone occurs in two polymorphic forms, it is unsaturated and yields a dioxime. It reacts with hydrogen, taking up three molecules to form the corresponding saturated substance, and the two ketonic groups are converted into alcoholic groups. This

[1] Ruzicka et al., *Helv. Chim. Acta*, 1934, 17, 1395.

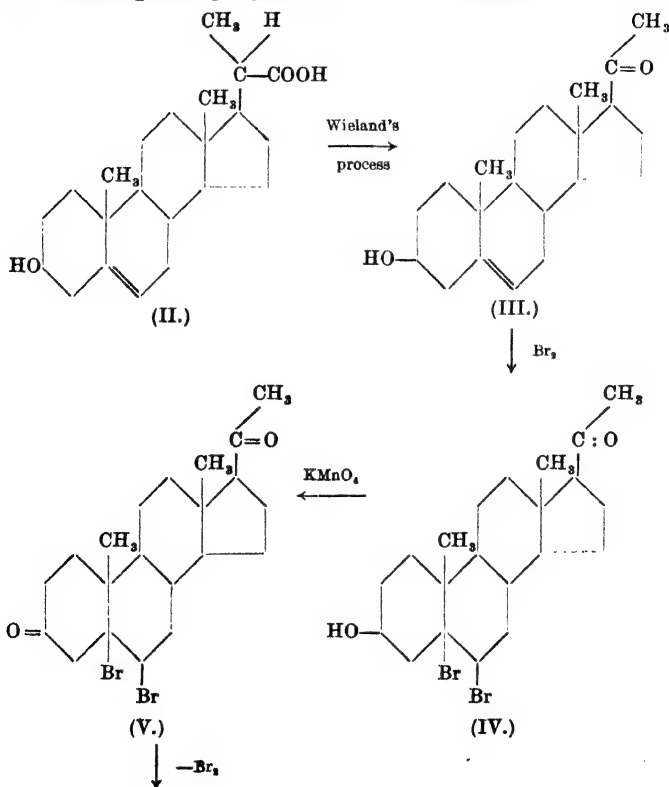
indicates the presence of one double bond in the molecule.[1] The relationship of progesterone to oestrone and to stigmasterol is very close, and the preparation of the hormone from both pregnanediol and stigmasterol gives a clear picture of the progesterone structure.

The compound 3-hydroxy*bisnor*cholenic acid (II.), which can be obtained from stigmasterol, is converted into the hydroxy ketone (III.) by Wieland's method (see page 12). The dibromide (IV.) of the hydroxy ketone on oxidation with permanganate yields the diketo-dibromide (V.). On eliminating the bromine from this compound progesterone (VI.) is formed.[2]

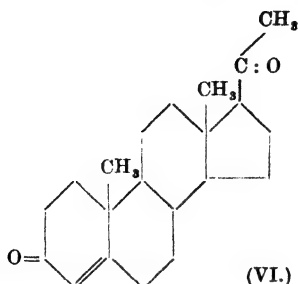
(II.) —Wieland's process→ (III.)

(III.) —Br_2→ (IV.)

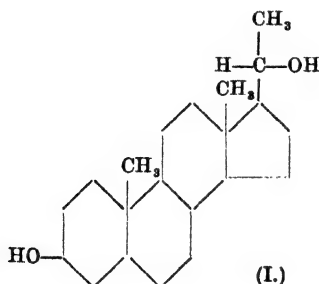
(IV.) —$KMnO_4$→ (V.)

(V.) —$-Br_2$→

[1] Butenandt and Westphal, *Ber.*, 1934, **67**, [B], 1440; *Z. physiol., Chem.*, 1934, **227**, 84; Slotta, Ruschig, and Fels, *Ber.*, 1934, **67**, [B], 1270, 1624; Hartmann and Wettstein, *Helv. Chim. Acta*, 1934, **17**, 878, 1365.

[2] Fernholz, *Ber.*, 1934, **67**, 1855; Butenandt, Westphal, and Cobler, *ibid.*, 1611.

CH₃ C : O CH₃ CH₃ O= (VI.)

These changes show the presence in the progesterone molecule of the pentenophenanthrene skeleton. It also fixes the positions of the side-chain and the ketonic groups. The position of the double carbon bond is at either $C_{4:5}$ or $C_{5:6}$. The preparation of progesterone from pregnanediol fixes the position of the double bond with reasonable certainty.

Pregnanediol, a compound closely related to oestrone, and occurring along with it in extracts of urine, has been proved to be a di-secondary alcohol with the pentenophenanthrene skeleton in the molecule. It has been given the structure,

CH_3 H—C—OH CH_3 CH_3 HO— (I.)

Pregnanediol diacetate (II.) can be partially hydrolysed[1] to yield the side-chain monoacetate (III.) which, on oxidation and hydrolysis, is converted into pregnaneolone (3) (IV.). This substance, on treatment with bromine in acetic acid solution, is converted by substitution into the monobromo compound (V.). Oxidation of this yields the corresponding bromo diketone (VI.), which, on treatment with boiling pyridine, splits off H and Br to yield progesterone (VII.). The following diagram will make the steps clearer :

[1] Butenandt and Schmidt, *Ber.*, 1934, 67, [B], 1901.

CH_3 | H—C.O.CO.CH_3 | CH_3 | CH_3 | CH_3CO.O— | H | H

(II.)

Partial hydrolysis →

CH_3 | H—C—O.CO.CH_3 | CH_3 | CH_3 | HO— | H | H

(III.)

↓ Oxidation and hydrolysis

CH_3 | H—C—OH | CH_3 | CH_3 | O= | H | H

(IV.)

← Bromination

H, CH_3, C, OH | CH_3 | CH_3 | O= | H | Br

(V.)

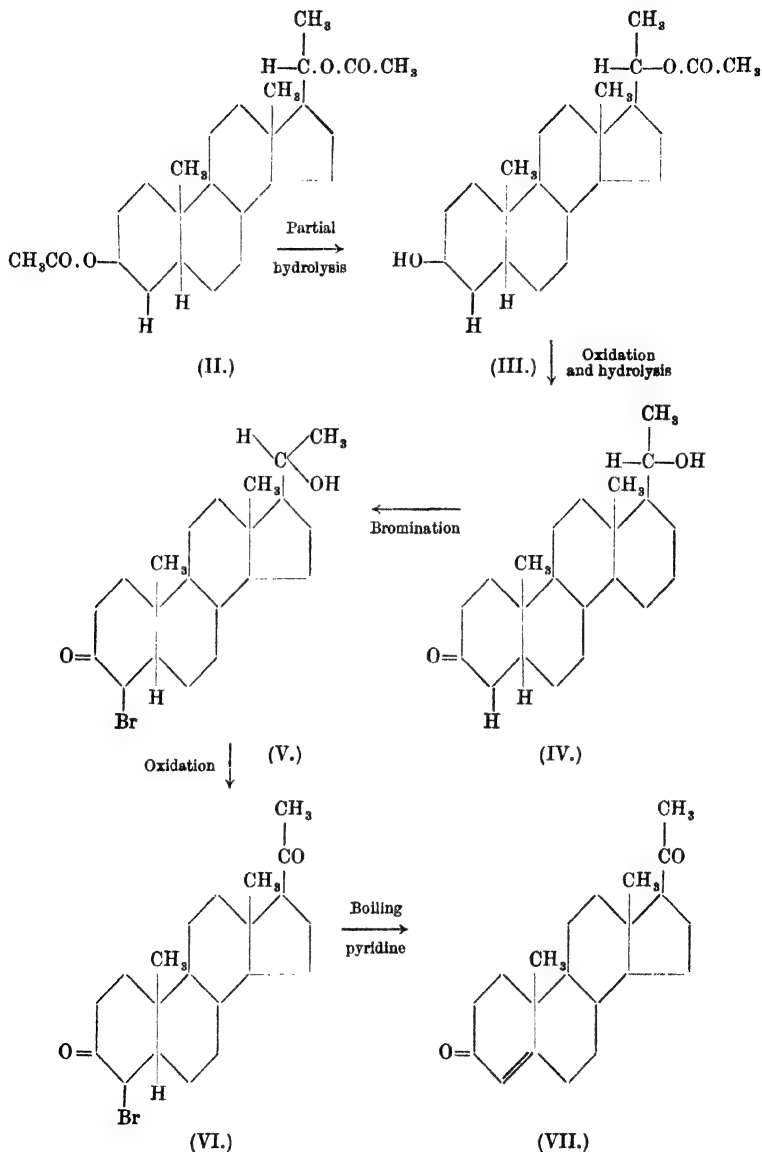
Oxidation ↓

CH_3 | CO | CH_3 | CH_3 | O= | H | Br

(VI.)

Boiling pyridine →

CH_3 | CO | CH_3 | CH_3 | O=

(VII.)

The formation of progesterone from stigmasterol and pregnanediol derivatives leaves very little doubt about the position of the double carbon bond in the hormone. The conclusion to

be drawn from the stigmasterol preparation is that the double bond is at $C_5 : C_6$ or, if the wandering of the double bond is assumed, at position $C_4 : C_5$. In the preparation from pregnanediol the bromine atom could have entered at position 2, leading to a final product with the double bond at $C_1 : C_2$. This structure, however, is ruled out by the preparation from stigmasterol. The evidence obtained from the absorption spectrum of progesterone indicates that the double bond is conjugated with one of the keto groups. The weight of all the evidence is, therefore, in favour of position $C_4 : C_5$ for the double bond.

F.—The Plant Hormones, Auxin-*a* and Auxin-*b*

1. *Introductory*

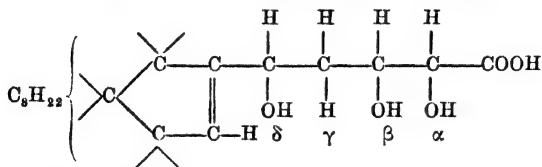
Animal growth takes place almost entirely by cell multiplication. In plants, however, both cell division and cell extension play a part. The increase in volume in higher plants depends principally on cell extension. This extension takes place under the influence of definite growth substances,[1] which have been named auxins.[2] These active substances are formed in the tip of the plant seedlings and migrate downwards to the base. If the tip of the seedling is removed a condition of deficiency is induced, the outcome being an interruption of extensional growth for a time. New growth can be brought about by auxins from various sources. Auxin-*a* was discovered in relatively high concentration in human urine, and it was from this source that it was first isolated along with its lactone.[3] Auxin-*a* has also been isolated from maize germ oil and from malt. In addition, an active compound has been obtained from malt. This is known as auxin-*b*.

2. *The Structures of Auxin-a and Auxin-b*

The molecular formula given to auxin-*a* is $C_{18}H_{32}O_5$. It is a monobasic acid containing, in addition, three hydroxyl groups and one double bond.

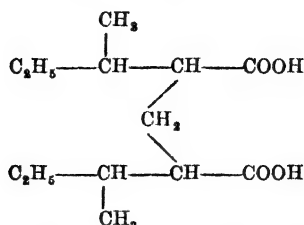
[1] Went, *Rec. trav. botan. néerland.*, 25, 1, (1928).
[2] Kögl and Haagen-Smit, *Proc. Acad. Wetenschappen Amsterdam*, 34, 1411, (1931).
[3] Kögl, Haagen-Smit, and Erxleben, *Z. physiol. Chem.*, 314, 241 (1933).

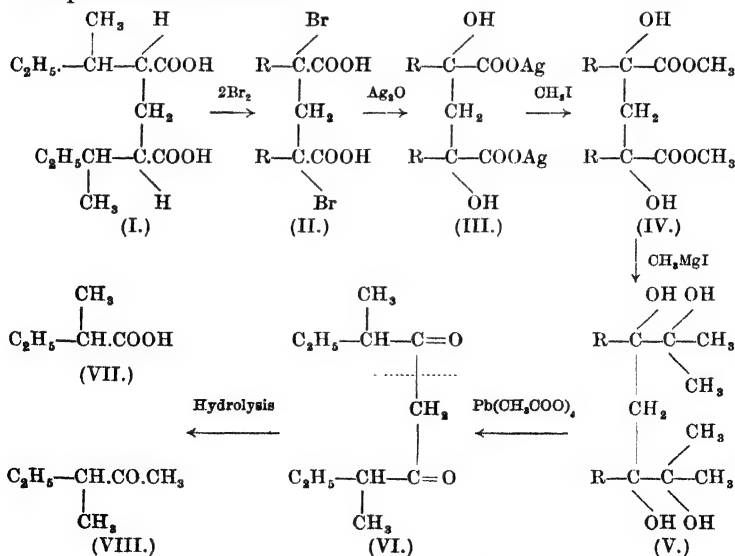
Hydrogenation yields a dihydro-compound, $C_{18}H_{34}O_5$, and consequently the presence of one ring in the molecule is inferred, since a straight chain saturated compound would have the formula, $C_{18}H_{36}O_5$. Auxin-*a* is optically active and shows muta-rotation owing to lactone formation.[1] Equilibrium of the acid and lactone is reached in a few hours, and it is concluded from this that there is an hydroxyl group in the δ position to the carboxyl.[2] Oxidation of auxin-*a* with alkaline permanganate yields a dibasic acid, $C_{13}H_{24}O_4$. This acid, on pyrolysis, behaves as a glutaric acid derivative, forming an anhydride. Auxin-*a* is not enolic in character, so that the double bond cannot be in the γ : δ position relative to the carboxyl group, that is, adjacent to the δ-hydroxyl group. If the double bond were in the position β : γ, oxidation would have yielded a malonic acid derivative. Similarly, the α : β position for the double bond may be rejected as an α-keto-acid would have been obtained on oxidation. It is, therefore, concluded that the original carboxyl group of auxin-*a* disappears in the five carbon atoms split off by oxidation, and that two new carboxyl groups come into existence when the acid $C_{13}H_{24}O_4$ is formed. It follows that the double bond must be in the auxin-*a* ring, otherwise both carboxyl groups, arising from the double bond, could not remain in the molecule. This conclusion is supported by the fact that the dihydro-auxin-*a* yields only a ketone on oxidation. Here also the five-carbon residue is eliminated, but the ring is not opened.

The foregoing facts may be expressed as follows :

The five-carbon residue is attached to one of the carbons bearing the double bond and a hydrogen must be attached to the other double bond carbon atom to account for the formation of the dibasic acid on oxidation.

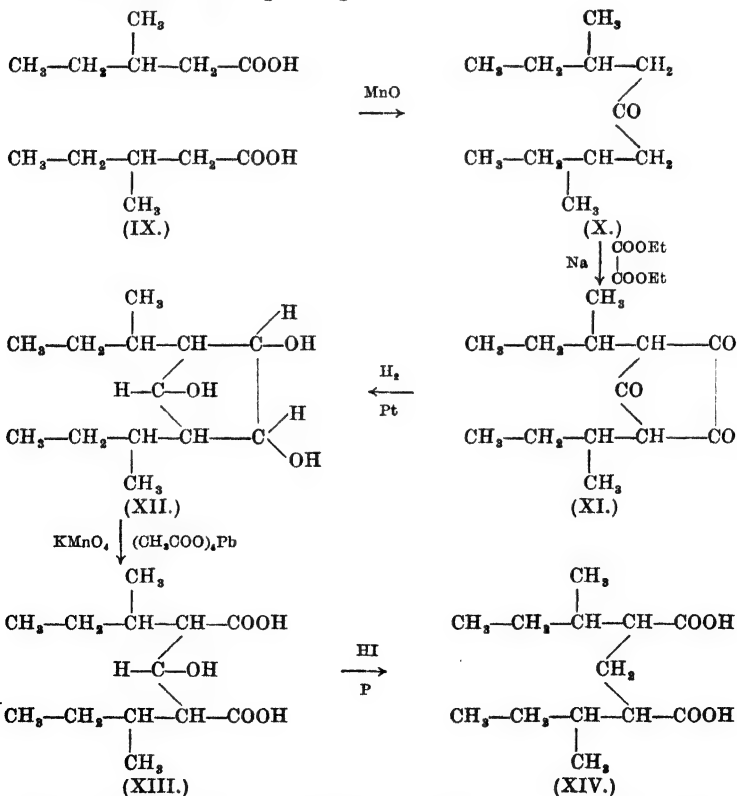
The acid, $C_{13}H_{24}O_4$, has been identified [3] as αα′-di-*sec*-butylglutaric acid,

[1] Kögl, *Naturwiss*, 1933, 21, 17.
[2] Kögl, *Angew. Chem.*, 1933, 46, 469.
[3] Kögl and Erxleben, *Z. physiol. Chem.*, 1934, 227, 51.

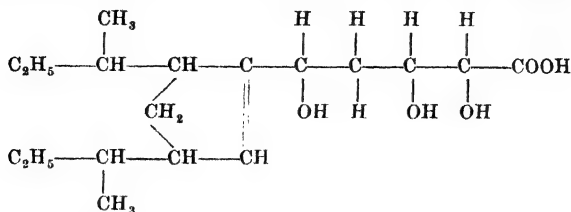
```
               CH3
               |
C2H5——CH——CH——COOH
              /
           CH2
              \
C2H5——CH——CH——COOH
           |
           CH3
```

The structure of this compound has been proved by a study of its fission products and by its synthesis. The scheme of degradation is as follows: αα′-di-*sec*-butylglutaric acid $C_{13}H_{24}O_4$ (I.), was dibrominated, then treated with silver oxide, and the silver salt of the dihydroxy acid (III.) acted upon with methyl iodide. The ester (IV.) formed was allowed to interact with methyl magnesium iodide. The glycol (V.) produced, when treated with lead tetra-acetate, yielded an optically active β-diketone (VI.).[1] Hydrolysis of the diketone gave rise to dextro-rotatory α-methyl butyric acid (VII.), and methyl *sec*-butyl ketone (VIII.). The last products were homogeneous, so the diketone must have been symmetrical. These changes may be represented as follows:

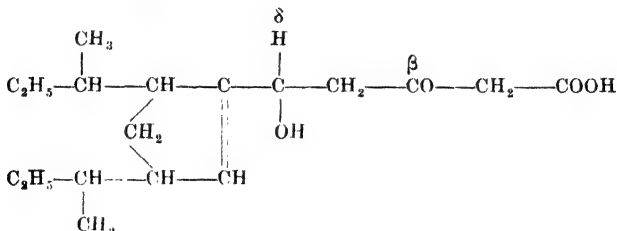
```
  CH3   H                Br              OH                 OH
  |    /                /               /                  /
C2H5.—CH—C.COOH      R—C.COOH       R—C—COOAg          R—C—COOCH3
         |      2Br2    |      Ag2O     |       CH3I       |
         CH2    ---->   CH2    ---->    CH2     ---->      CH2
         |              |               |                  |
C2H5CH—C.COOH        R—C.COOH       R—C—COOAg          R—C—COOCH3
   |     \               \               \                  \
   CH3    H               Br              OH                 OH
     (I.)               (II.)           (III.)             (IV.)
                                                             | CH3MgI
                                                             v
   CH3                     CH3                             OH OH
   |                       |                               /  /
C2H5—CH.COOH          C2H5—CH—C=O                      R—C—C—CH3
  (VII.)                      |                          |   \
                        ......|......                    |    CH3
           Hydrolysis         CH2    Pb(CH3COO)4         CH2
        <------------         |      <------------       |    CH3
                              |                          |   /
C2H5—CH.CO.CH3        C2H5—CH—C=O                      R—C—C—CH3
     |                     |                              \   \
     CH3                   CH3                            OH OH
   (VIII.)                (VI.)                            (V.)
```

[1] Criegee, *Ber.*, 1931, **64**, 260; *Annalen*, 1932, **495**, 211; Criegee, Kraft and Rank, *ibid.*, 1933, **507**, 159; Karrer, Benz et al., *Helv. Chim. Acta*, 1932, **15**, 1399.

The synthesis of $\alpha\alpha'$-di-*sec*-butylglutaric acid was accomplished in the following way. 3-Methylvaleric acid (IX.) in an atmosphere of carbon dioxide was passed over heated manganous oxide and converted into the ketone (X.). By the action of sodium and ethyl oxalate this ketone yielded the *cyclo*pentane triketonic derivative (XI.), which was catalytically reduced to the corresponding triol (XII.). Oxidation of the trihydroxy compound yielded the hydroxyglutaric acid derivative (XIII.). Reduction of this compound by means of hydriodic acid and red phosphorus yielded a mixture of isomeric $\alpha\alpha'$-di-*sec*-butylglutaric acids (XIV.). When the mixture was resolved by means of the brucine and cinchonidine salts, one of the stereo-isomers proved to be identical with the acid obtained by oxidation from auxin-*a*.[1] The structural steps are given below.

```
           CH3                                                CH3
           |                                                  |
CH3—CH2—CH—CH2—COOH                              CH3—CH2—CH—CH2
                                  MnO                            /
                                 ---->                         CO
                                                                 \
CH3—CH2—CH—CH2—COOH                              CH3—CH2—CH—CH2
           |                                                  |
           CH3                                                CH3
          (IX.)                                              (X.)
                                                          |  COOEt
                                                       Na |  |
                                                          v  COOEt
           CH3                                                CH3
           |           /H                                     |
CH3—CH2—CH—CH———C—OH                             CH3—CH2—CH—CH———CO
              /         |            H2                      /        |
         H—C—OH         |           <----                  CO         |
              \         |  /H        Pt                      \        |
CH3—CH2—CH—CH———C<                               CH3—CH2—CH—CH———CO
           |               \OH                                |
           CH3                                                CH3
          (XII.)                                             (XI.)
 KMnO4 |  (CH3COO)4Pb
       v
           CH3                                                CH3
           |                                                  |
CH3—CH2—CH—CH—COOH                               CH3—CH2—CH—CH—COOH
              /                       HI                     /
         H—C—OH                      ---->                CH2
              \                       P                      \
CH3—CH2—CH—CH—COOH                               CH3—CH2—CH—CH—COOH
           |                                                  |
           CH3                                                CH3
          (XIII.)                                            (XIV.)
```

[1] Kögl, Erxleben, Michaelis, and Visser, *Z. physiol. Chem.*, 1935, **235**, 181.

This allows the structure of auxin-*a* to be formulated as :

```
       CH3                     H    H    H    H
       |                       |    |    |    |
C2H5——CH————CH————C————C————C————C————C————COOH
            /     ||   |    |    |    |
         CH2      ||   OH   H    OH   OH
            \     ||
C2H5——CH————CH————CH
       |
       CH3
```

Auxin-*b* has the molecular formula $C_{18}H_{30}O_4$. It contains a carboxyl group and one hydroxyl. Its mutarotation indicates that it is a δ-hydroxy acid. The fourth oxygen atom is present in a keto group. As auxin-*b* readily evolves carbon dioxide when heated to its melting point, it is inferred that it is a β-ketonic acid. On oxidation with permanganate auxin-*b* yields αα′-di-*sec*-butylglutaric acid. Therefore the major portion of the molecule, including the unsaturated ring, is the same as in auxin-*a*. Summing up the properties of auxin-*b* its formula may be written as :

```
                               δ
       CH3                     H
       |                       |          β
C2H5——CH————CH————C————C————CH2————CO————CH2————COOH
            /     ||   |
         CH2      ||   OH
            \     ||
C2H5——CH————CH————CH
       |
       CH2
```

Another active substance has been isolated and turns out to be identical with β-indolylacetic acid.[1] Its physiological activity is much the same as that of the auxins. Indole itself is inactive, but other related compounds possess activity. In this connection interesting results have been recorded in connection with skatole. A series of experiments show that skatole has a growth-promoting effect on decapitated coleoptiles of oat seedlings.[2] A root-producing hormone has been discovered. This substance, known as rhizocaline, is said to be similar to the auxins in chemical properties, but not identical with either auxin-*a* or auxin-*b*.[3]

[1] Kögl, Haagen-Smit and Erxleben, *Z. physiol. Chem.*, **228**, 90, 104 (1934).

[2] Glover, *Nature*, **1936**, **137**, 320.

[3] Bouillenne and Went, *Ann. jardin. botan. Buitenzorg*, **43**, 1 (1933); Went. *Z. Botan.*, **23**, 19 (1933); Went, *Proc. Acad. Wetenschappen Amsterdam*, **37**, 445 (1934); Thimann and Went, *ibid.*, **37**, 456 (1934).

CHAPTER IV

THE CARDIAC AGLYCONES

(THE VEGETABLE HEART POISONS)

A.—Introductory

Digitoxin from the leaves, and digitalin from the seeds of *Digitalis purpurea*, squill, strophanthin and apocynum, are well-known medicinal substances, valuable on account of their tonic action on the heart. They contain mixtures of glycosides, but until recently chemical investigation had not yielded definite results on their constitutions. The aglycones may be isolated from the more complex substances by hydrolysis with acid or enzymes. A number of these aglycones have been characterized and shown to contain the *cyclo*pentenophenanthrene framework in their molecular structures. The compounds which have received most attention are strophanthidin, $C_{23}H_{32}O_6$; uzarigenin, $C_{23}H_{34}O_5$; periplogenin, $C_{23}H_{34}O_5$; digitoxigenin, $C_{23}H_{34}O_5$; gitoxigenin, $C_{23}H_{34}O_5$; scillaridin A, $C_{25}H_{32}O_3$. The known facts point to their close relationship to one another, and to the bile acids and sterols.

B.—The Structure of Strophanthidin

The glycoside strophanthin on acid hydrolysis yields the aglycone.[1] The aglycone has been shown to contain a lactone ring in the form of an unsaturated side-chain, which can be removed by oxidation to form an acid.

Three hydroxyls and an aldehyde group are also present, and one of the hydroxyls is in a secondary alcoholic group.[2]

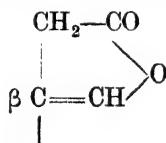
Dehydrogenation of both strophanthidin and uzarigenin [3]

[1] Jacobs and Hoffmann, *J. Biol. Chem.*, 1926, **67**, 609; **69**, 153; Windaus and Herrmanns, *Ber.*, 1915, **48**, 979, 991.

[2] Jacobs et al., *J. Biol. Chem.*, 1922, **54**, 253; 1924, **59**, 713; 1925, **65**, 491; 1927, **74**, 805.

[3] Tschesche and Knick, *Z. physiol. Chem.*, 1933, **222**, 58; Jacobs and Elderfeld, *Sci.*, 1934, **79**, 279; *J. Biol. Chem.*, 1934, **107**, 143; Jacobs and Fleck, *Sci.*, 1931, 133; *J. Biol. Chem.*, 1932, **97**, 57.

leads to Diels's Hydrocarbon (3′-methyl-1 : 2-*cyclo*pentenophenanthrene), and degradations of derivatives of uzarigenin, digitoxigenin and scillaridin A produce cholanic acid compounds.[1] The molecular framework of these substances is therefore the same as in the bile acid and sterols.

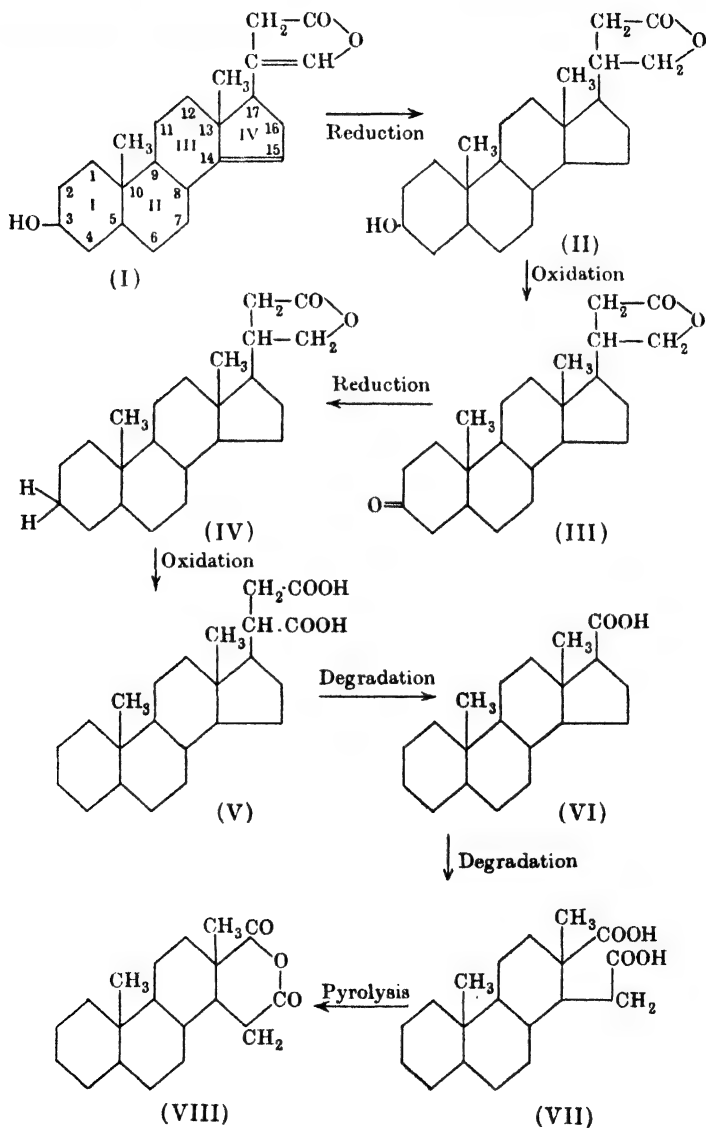
The lactone ring unsaturated side-chain, which is present in all the aglycones of the strophanthidin group, contains four carbon atoms. Strophanthidin and some of its relatives show the characteristic colour reactions of Δ^{β}-unsaturated lactones, and the ring does not undergo fission on reduction. For these reasons the side-chain ring has been given the structure,

and the attachment to the remainder of the molecule made through the β-carbon atom. When the lactone ring is opened an aldehyde group is formed. Strophanthidin and its relatives undergo a characteristic change when acted on with alkali,[2] isomerisation takes place, one of the hydroxyl groups attached to a neighbouring carbon atom is involved, and the ring becomes saturated (*see* digitoxigenin, VII. and VI.). The lactone ring is attached to ring IV. at the point C_{17}. This was shown to be correct by the production of *allo*-aetiocholanic acid from an uzarigenin derivative.

Reduction of anhydrouzarigenin, which may be represented as (I.), yielded a tetrahydro-compound (II.) containing a secondary alcoholic group. Oxidation produced a ketone (III.), which on reduction gave two desoxy lactones (IV.). These compounds when oxidized formed two stereoisomeric dibasic acids, $C_{23}H_{36}O_4$ (V.), by the opening of the lactone ring. When degraded by the Grignard reaction, followed by oxidation, *allo*-aetiocholanic acid, $C_{20}H_{32}O_4$ (VI.), was isolated.[3] Further degradation of *allo*aetiocholanic acid yielded a dibasic acid (VII.)

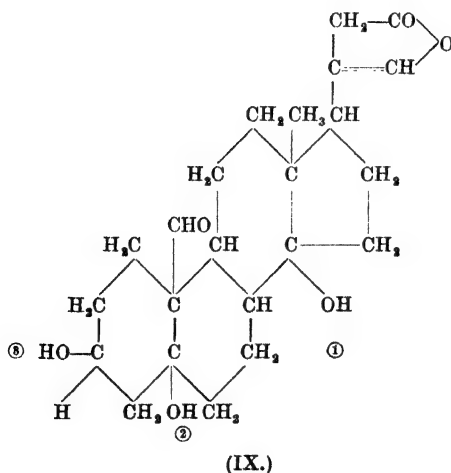
[1] Tschesche, *Ber.*, 1935, **68**, [B], 7; Jacobs and Elderfield, *Sci.*, 1934, **80**, 533; *J. Biol. Chem.*, 1935, **108**, 497; Stoll, Hofmann and Helfenstein, *Helv. Chim. Acta*, 1935, **18**, 644.

[2] Jacobs et al., *J. Biol. Chem.*, 1924, **61**, 387; 1926, **70**, 1; 1927, **74**, 787; 1930, **87**, 601; 1931, **93**, 139.

[3] Tschesche, *Z. physiol. Chem.*, 1934, **229**, 219.

by the opening of the ring. As this new acid was from a terminal ring and formed an anhydride (VIII.) on pyrolysis, it was concluded that the carbon ring was a five-membered one. These changes may be represented as follows :

The hydroxyl groups of strophanthidin, which are not involved in the formation of the *iso*-compound by the action of alkali, are considered to be situated in the β-position relative to one another from the study of the dehydration reactions of strophanthidin and its ketonic derivatives.[1] Parallel with the bile acids and sterols, one hydroxyl group has been allocated to position C_3, and the other to C_5. The aldehyde group of strophanthidin has been placed at the quaternary atom C_{10}. This seems the most suitable position for the group as a methyl group is present in this position in uzarigenin. Both aglycones yield Diels's Hydrocarbon, which involves the disappearance of the aldehyde group in one case and the methyl group in the other; the elimination of these groups during the dehydrogenation to Diels's Hydrocarbon is most satisfactorily accounted for by assuming that they were attached to a quaternary carbon atom.[2] The structure of strophanthidin may now be written down (IX.):

```
                              CH2—CO
                              |       >O
                              C=====CH
                              |
                         CH2 CH3 CH
                H2C          C          CH2
                CHO
          H2C        CH      C ———— CH2
      H2C       C       CH       OH
 (3) HO—C       C       CH2      (1)
    H       CH2 OH CH2
                (2)
```

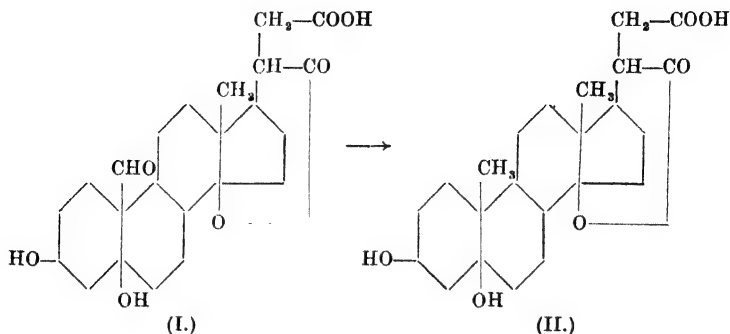
(IX.)

[1] Jacobs and Gustus, *J. Biol. Chem.*, 1927, **74**, 713.
[2] Kon, *J. Soc. Chem. Ind.*, 1934, 593, 956, 1008.

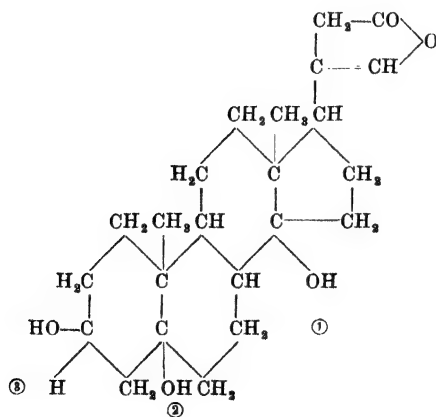
C.—The Structure of Periplogenin

When the semicarbazone of *iso*strophanthidic acid (I.) is reduced by the Wolff[1] method *iso*periplogenic acid[2] (II.) is formed :

CH_2—COOH
CH—CO
CH_3
CHO
O
HO—
OH
(I.)

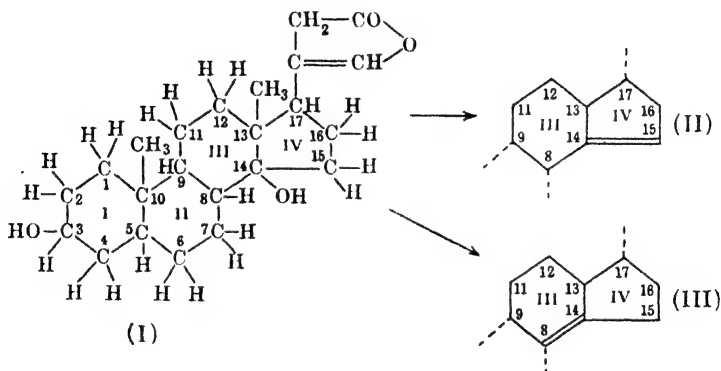
→

CH_2—COOH
CH—CO
CH_3
CH_3
O
HO—
OH
(II.)

It is concluded, therefore, that the structure of periplogenin is (III.),

CH_2—CO
O
C — CH
CH_2 CH_3 CH
H_2C C CH_2
CH_2 CH_3 CH C—CH_2
H_2C C CH OH
HO—C C CH_2 ①
③ H CH_2 OH CH_2
②

a methyl group taking the place of the aldehyde group of strophanthidin at the position C_{10}.

[1] Wolff, *Annalen*, 1912, **394**, 86.
[2] Jacobs et al., *J. Biol. Chem.*, 1931, **91**, 617.

D.—The Structure of Uzarigenin

This compound has been isolated in the form of the mono-anhydro-derivative, $C_{23}H_{32}O_3$. Two of the oxygen atoms are accounted for by the lactone ring, so that uzarigenin itself contains only two hydroxyl groups. Uzarigenin (I.) gives rise to two mono-anhydro-derivatives, known as α- and β-anhydro-uzarigenin, by the loss of a tertiary hydroxyl group. The formation of these two substances is explained by placing the hydroxyl group of uzarigenin at carbon atom 14, and assuming that the ethylene linkage, arising from the elimination of the elements of water, is, in the case of the α-compound (II.), between carbon atoms 14 and 15, and in the case of the β-compound (III.) between atoms 14 and 8.[1]

Position 14 for the tertiary hydroxyl group is supported by the fact that uzarigenin in the form of its glycoside (uzarin) yields an *iso*-derivative by the successive actions of methyl alcoholic potassium hydroxide and acetic acid.[2]

The structural relationship with periplogenin has been demonstrated in the following way: periplogenin (IV.) was heated with dilute methyl alcoholic hydrochloric acid, when a trianhydro-derivative was formed. This substance, which may be represented as (V.), was catalytically reduced to a mixture of isomeric octahydrotrianhydroperiplogenins (VI.), one of which

[1] Windaus and Haack, *Ber.*, 1930, **63**, 1377; Tschesche, *Z. physiol. Chem.*, 1933, **222**, 50.

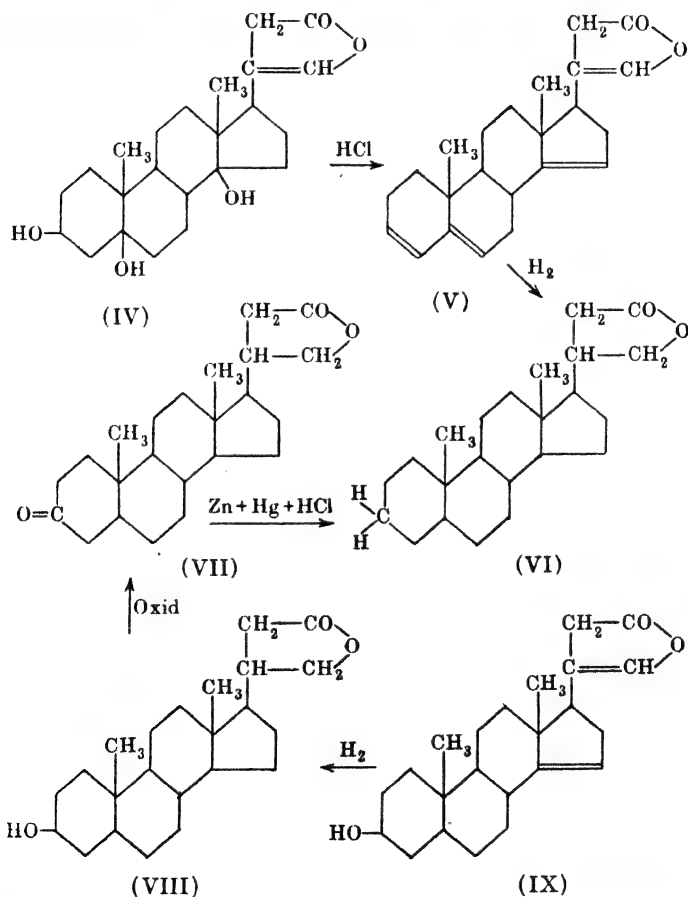
[2] Tschesche, Bohle, and Sab, *Ber.*, 1935, **68**, 2252.

was isolated in a pure condition. This same compound was obtained from α-anhydrouzarigenin (IX.) by the following steps. The acetate of the α-anhydro-compound was hydrogenated to the two stereisomeric tetrahydro-derivatives (VIII.). Oxidation of these yielded the corresponding ketones (VII.). The ketones were reduced by amalgamated zinc and hydrochloric acid (Clemmensen method) to the saturated lactones (VI.), one of which was identical with the octahydro-derivative from periplogenin.[1] The structural steps are as follows.

(IV) —HCl→ (V) —H_2→ (VI)

(VII) —Zn + Hg + HCl→ (VI)

(VIII) —Oxid→ (VII)

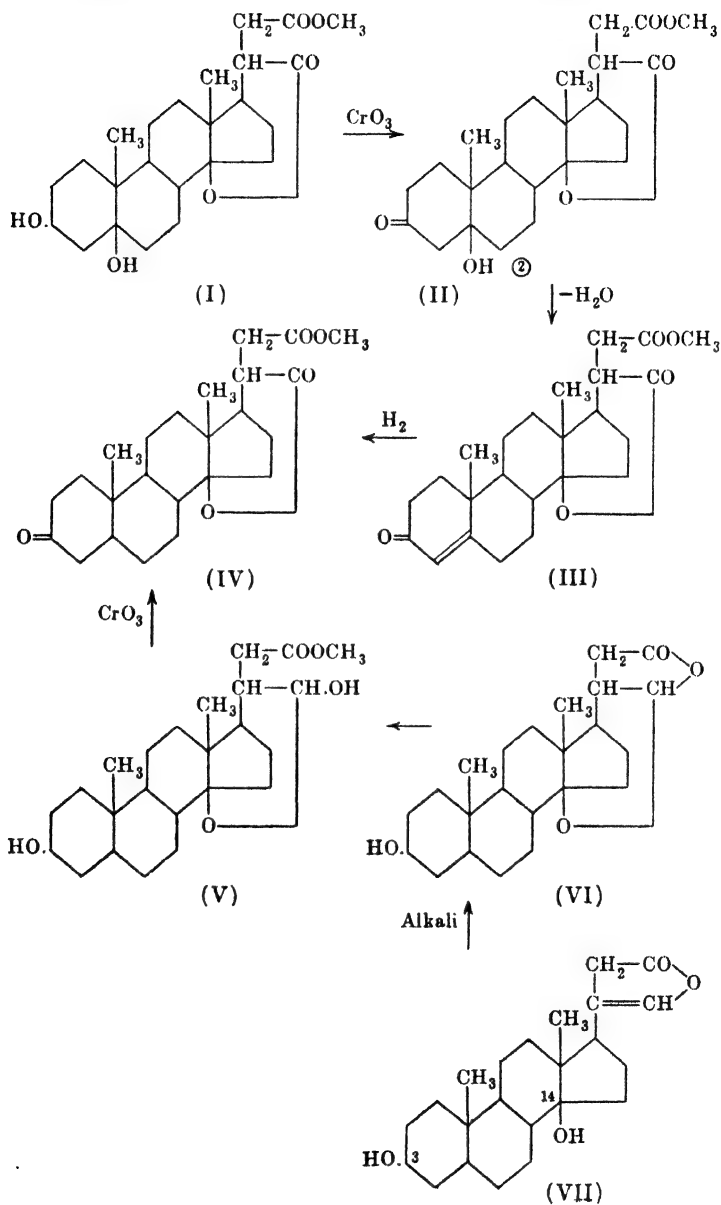
(IX) —H_2→ (VIII)

[1] Jacobs and Bigelow, *J. Biol. Chem.*, 1933, **101**, 697; Tschesche, *Z. physiol. Chem.*, 1933, **222**, 50.

In accordance with these views uzarigenin itself is formulated as (I.), and its degradation to *allo*-aetiocholanic acid proves it to have the *trans* or cholestanol configuration (see pp. 3 and 30).[1]

E.—The Structure of Digitoxigenin

When the methyl ester of *iso*periplogenic acid (I.) is oxidized with chromic acid to the ketonic ester (II.) and dehydrated by the elimination of the hydroxyl group ②, the anhydro-compound (III.) is formed. This, on hydrogenation, gave two stereoisomeric dihydro-compounds (IV.).[2] One of these isomers is identical with an ester derived from digitoxigenin (VII.) by isomerization (VI.) followed by opening of the lactone ring, esterification (V.) and finally oxidation (IV.) with chromic acid. The formulae on page 124 show the steps in these degradations.

[1] Tschesche, *Z. Angew. Chem.*, 1934, **47**, 729; *Z. physiol. Chem.*, 1934, **229**, 219; *Ber.*, 1935, **68**, 7.

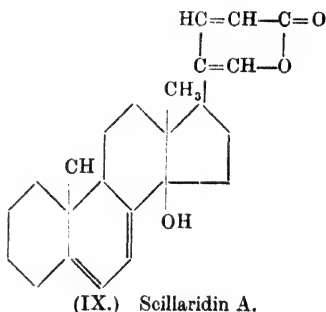
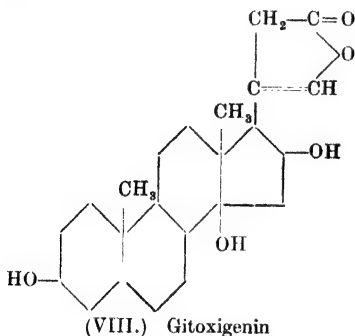
[2] Jacobs and Elderfield, *Science*, 1934, **80**, 434; *J. Biol. Chem.*, 1935, **108**, 497.

Digitoxigenin then has the same general structure as periplogenin, but has two hydroxyl groups only, attached at the points C_3 and C_{14}.

Digitoxigenin is isomeric with uzarigenin but its relationship to aetiocholanic acid shows that its configuration is of the *cis* or coprostanol type (see pp. 3 and 30).

F.—Gitoxigenin and Scillaridin A

Other compounds of this group are gitoxigenin and scillaridin A. Structure (VIII.) has been given to gitoxigenin,[1] and structure (IX.) suggested as a provisional representation of scillaridin A.[2]

(VIII.) Gitoxigenin

(IX.) Scillaridin A.

Other substances are known having an action on the heart similar to that of digitalis. Of these certain compounds isolated from the secretions of the glands of toads have been investigated and found to be structurally related to the vegetable heart poisons.[3]

[1] Jacobs et al., *J. Biol. Chem.*, 1928, **79**, 553 ; 1929, **82**, 403 ; 1930, **86**, 199 ; 1930, **88**, 531 ; 1933, **100**, 671.

[2] Stoll et al., *Helv. Chim. Acta*, 1933, **16**, 703 ; 1934, **17**, 641, 1334 ; 1935, 18, **92**, 401, 644, 1247 ; *Z. physiol. Chem.*, 1933, **222**, 24.

[3] Wieland et al., *Ber.*, 1913, **46**, 3315 ; 1922, **55**, 1789 ; *Annalen*, 1932, **493**, 272 · *ibid.*, 1935, 517, 22.

CHAPTER V

SOME NATURAL PORPHYRINS AND RELATED COMPOUNDS

A.—Introductory

The porphyrins are very widespread in nature, and when it is realized that haematin and chlorophyll fall into this group of compounds it is probably correct to say that the porphyrins are universal constituents of protoplasm. As is well known the function of haemoglobin in the blood is to carry oxygen from the lungs to different parts of the body. The porphyrin haematin is an essential part of haemoglobin and it is the iron atom of the haematin molecule which, readily changing from the ferrous to the ferric state, fixes one atom of oxygen and then parts with it to the tissues of the body. Haematin is not the only iron porphyrin which occurs in the human body; others such as the peroxidases, the cytochromes and catalase are also present and take part in the oxidations of the cells.

The bile pigments are closely related to haemoglobin. They are formed principally in the liver; and bilirubin, the best known member of this group, is derived mainly from haemoglobin by red cell degradation.

Chlorophyll, a magnesium porphyrin, plays an essential part in the photosynthesis of carbohydrates in the green leaves of plants. In addition to the iron and magnesium porphyrins other metallic derivatives are found in nature. Thus turacin, a pigment from the feathers of certain birds, contains a copper porphyrin, and it has been claimed that manganese and vanadium porphyrins have also been identified from natural sources.

B.—Haemin

1. *General*

The red blood corpuscles of mammals are made up of two parts, haemoglobin and a nucleo-protein in loose combination.

The two components may be separated by treatment with ether or by alternately freezing and thawing blood.

Oxyhaemoglobin can readily be obtained in a crystalline form, and separated by the action of glacial acetic acid into the colouring matter haematin and the protein globin. Haematin has the molecular formula $C_{34}H_{32}O_4N_4Fe.OH$. The chloride of this compound is haemin, $C_{34}H_{32}O_4N_4Fe.Cl$. Haemin can also be obtained directly from blood by heating with glacial acetic acid and sodium chloride. By the action of hydriodic acid and phosphonium iodide the haemin molecule is reduced and broken up to yield simple pyrrole homologues (I. to IV.). On the other hand if tin and hydrochloric acid are employed, some pyrrole carboxylic acids (V. to VIII.) are amongst the products of degradation. Comparatively mild reduction of haemin by means of sodium hydrosulphite in alkaline solution leads to the base with the iron atom in the ferrous condition. This compound is known as haem and is regarded as the coloured component of haemoglobin itself (reduced haemoglobin).

Oxidation of haemin (XXIII.) leads to haematic acid (IX.). During the process the two pyrrole nuclei carrying vinyl groups are completely degraded, the other two nuclei giving rise to the acid. If haemin is first reduced and then oxidized, methyl ethyl maleinimide (X.) appears as one of the products.

The action of hot potassium methoxide on haemin under pressure also breaks down the molecule to simple pyrrole derivatives, the two main products being phyllopyrrole, $C_9H_{15}N$ (XI.) and phyllopyrrole carboxylic acid, $C_{10}H_{15}O_2N$ (XII.). The foregoing facts show that pyrrole nuclei form an important part of the haemin molecule. A further point of great interest is that the treatment of haemin or haematin with sulphuric acid leads to the elimination of iron with the formation of haematoporphyrin, $C_{34}H_{38}O_6N_4$ (XXI.). If the iron be removed from haemin by the action of colloidal palladium or iron powder in the presence of formic acid, protoporphyrin, $C_{34}H_{34}O_4N_4$ (XXII.), is the product obtained.[1] Protoporphyrin is the parent porphyrin of haemin, as it contains the two vinyl groups and the other radicles of haemin intact. Other porphyrins prepared either directly or indirectly from blood are mesoporphyrin, $C_{34}H_{38}O_4N_4$, aetioporphyrin, $C_{32}H_{38}N_4$, and deuteroporphyrin, $C_{30}H_{30}O_4N_4$

[1] Fischer and Pützer, *Z. physiol. Chem.*, 1926, **154**, 39.

(XVIII.). The following diagram shows the structures of the simple pyrrole derivatives obtained by the degradation of haemin.

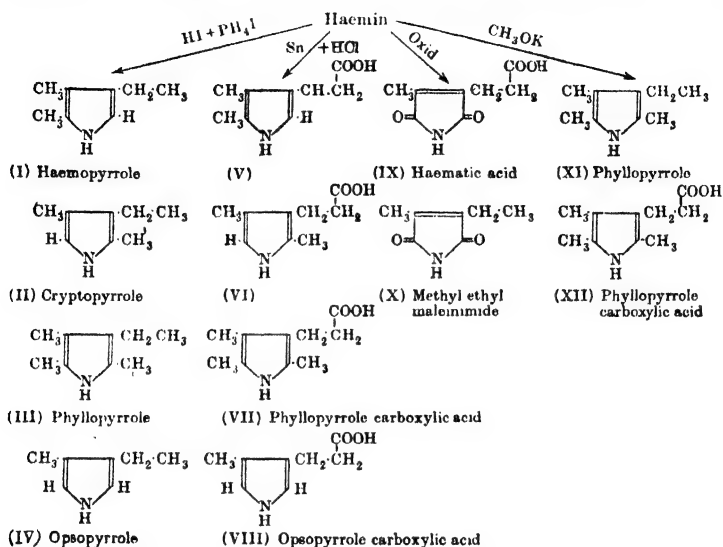
Haemin

HI + PH_4I — Sn + HCl — Oxid — CH_3OK

(I) Haemopyrrole (V) (IX) Haematic acid (XI) Phyllopyrrole

(II) Cryptopyrrole (VI) (X) Methyl ethyl maleinimide (XII) Phyllopyrrole carboxylic acid

(III) Phyllopyrrole (VII) Phyllopyrrole carboxylic acid

(IV) Opsopyrrole (VIII) Opsopyrrole carboxylic acid

2. *The Structure and Synthesis of Haemin*

Taking into consideration the molecular composition of haemin and the nature of the degradation products it is reasonable to conclude that the skeleton of the haemin molecule is made up of four pyrrole nuclei linked together. A cyclic arrangement of the four groups was proposed as far back as 1913.[1] This has been supported by later work which has, in addition, established beyond doubt the nature and positions of the substituents attached to the pyrrole nuclei.[2] The structure of haemin is shown on page 130 (XXIII.). As the iron atom is present in an unionizable condition, it is regarded as being held in complex combination.

Haemin, haematoporphyrin, protoporphyrin and deuteroporphyrin have been synthesized from simple pyrroles by methods which leave very little doubt about their structures. When

[1] Küster, *Z. physiol. Chem.*, 1913, **82**, 463.

[2] Fischer et al., *Annalen*, 1928, **466**, 178, 183; 1929, **473**, 245; 1931, **491**, 162, 173.

2:3-dimethylpyrrole (XIII) and 2:4-dimethylpyrrole-5-aldehyde (XIV) were condensed by means of an alcoholic solution of hydrogen bromide the methene hydrobromide (XV) was formed. Similarly carboxylic acid (XVI) on bromination and condensation yielded its methene hydrobromide (XVII). When the two methenes were heated to 180–190° C. with succinic acid deuteroporphyrin (XVIII) was formed. An atom of iron was introduced into the porphyrin by treating the glacial acetic acid solution of the free porphyrin with ferrous acetate mixed with some sodium chloride and a little concentrated hydrochloric acid. The deuterohaemin (XIX) thus formed was converted into the diacetyl derivative by the action of acetic anhydride and stannic chloride at ordinary temperature. Diacetyldeuterohaemin when acted upon by hydrogen bromide and glacial acetic acid was converted into diacetyldeuteroporphyrin (XX), which was converted into haematoporphyrin (XXI) by the action of boiling alcoholic potassium hydroxide. On vacuum distillation haematoporphyrin gave a quantitative yield of protoporphyrin (XXII). The addition of the calculated amount of ferric chloride in glacial acetic acid solution in the presence of sodium acetate converted protoporphyrin into haemin (XXIII). These synthetic porphyrins and haemin were identical with the corresponding products from blood.[1]

[1] Fischer and Zeile, 1929, **468**, 98.

C.—Bilirubin

1. *General*

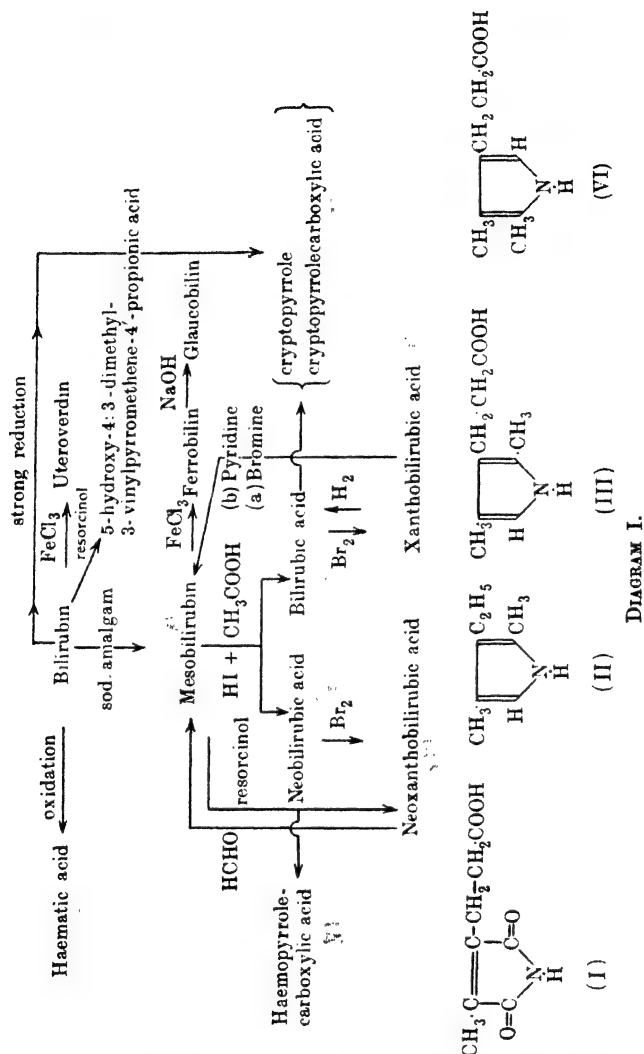
A number of pigments occur in bile. The most important is bilirubin, $C_{33}H_{36}O_6N_4$. Its molecular formula suggests a connection with the porphyrins, and this is borne out by the nature of the products of chemical decomposition. There is also considerable evidence that the pigment in the living animal is derived from haemoglobin. Bilirubin yields haematic acid (I.) on oxidation and cryptopyrrole (II.) and cryptopyrrolecarboxylic acid (III.) on strong reduction.[1] Milder reduction using sodium amalgam yields mesobilirubin, $C_{33}H_{40}O_6N_4$. This compound on reduction with hydriodic and acetic acids breaks down into the pyrromethanes, bilirubic acid, $C_{17}H_{24}O_3N_2$ (IV.) and neobilirubic acid, $C_{16}H_{22}O_3N_2$ (V.). Bilirubic acid on further reduction gives cryptopyrrolecarboxylic acid as the main product, whilst neobilirubic acid on similar treatment yields haemopyrrolecarboxylic acid (VI.).[2] Bilirubin does not give the characteristic absorption spectrum of a porphyrin and consequently it and mesobilirubin have been given open chain structures of four pyrrole nuclei linked together by carbon atoms.

The methane derivative, bilirubic acid, can be oxidized by bromine to the corresponding pyrromethene known as xanthobilirubic acid (VII.). Similarly, neobilirubic acid yields neoxanthobilirubic acid (VIII.)[3] These and some other transformations of the bilirubin compounds are summarized in diagram I.

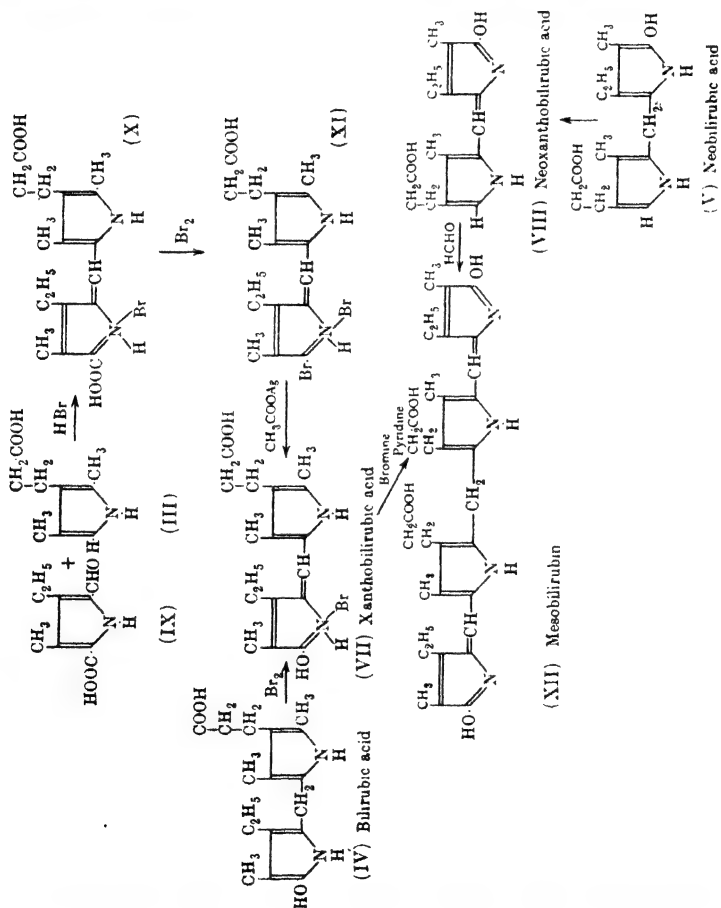
[1] Küster, *Z. physiol. Chem.*, 1898, **26**, 314; Fischer and Adler, *ibid.*, 1931, **197**, 237.

[2] Fischer and Hess, *Z. physiol. Chem.*, 1931, **194**, 201.

[3] Fischer and Rose, *Ber.*, 1913, **46**, 439.

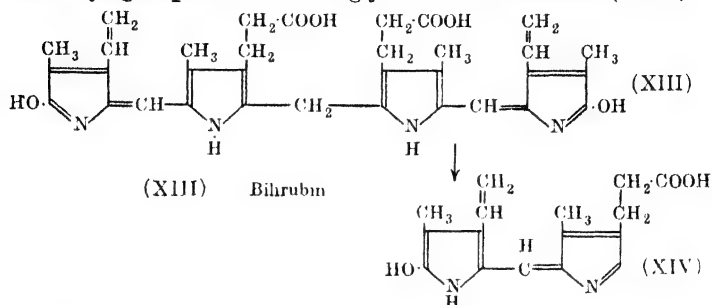
DIAGRAM I.

2. *The Structures of Bilirubin, Mesobilirubin and Xanthobilirubic Acid*

The structure of xanthobilirubic acid has been established by its synthesis from simple pyrrole derivatives of known structure. This synthetic xanthobilirubic acid has been converted into mesobilirubin identical with the product obtained

by the reduction of bilirubin from natural sources. 5-Aldehydo-3-methyl-4-ethylpyrrole-2-carboxylic acid (IX.) and cryptopyrrole carboxylic acid (III.) were condensed by the action of hydrobromic acid to yield 5-carboxy-4 : 3′ : 5′-trimethyl-3-ethylpyrromethene-4′-propionic acid hydrobromide (X.). This methene was converted into the 5-bromo-derivative (XI.) by the action of bromine. Silver acetate converted the 5-bromo-derivative into xanthobilirubic acid (VII.) from which mesobilirubin (XII.) was obtained by bromination followed by treatment with pyridine.[1] These changes may be formulated as follows.

[1] Fischer et al., *Annalen*, 1930, **482**, 189 ; *Z. physiol. Chem.*, 1931, **200**, 209.

Neoxanthobilirubic acid is given the structure (VIII.). It also can be converted into mesobilirubin, by condensation with formaldehyde. The foregoing evidence points to a symmetrical structure such as (XII.) for mesobilirubin and bilirubin containing two vinyl groups will accordingly have the structure (XIII.).

(XIII) Bilirubin

(XIV)

This structure is supported by the conversion of bilirubin by the action of boiling resorcinol into 5-hydroxy-4 : 3′-dimethyl-vinylpyrromethene-4′-propionic acid (XIV.).[1] As bilirubin itself has not yet been synthesized, structure (XIII.) must still be regarded as provisional. It will be noticed on making a comparison between the structures of haemin and bilirubin that fission of the porphyrin ring at one point would not yield this bilirubin with the β-substituents placed as shown in structure (XIII.). In the animal body further degradation of the porphyrin ring of haemoglobin followed by condensation would be necessary to yield this bilirubin.*

D.—Chlorophyll

1. *General*

The chemical constitution of the green colouring matter of plants offered a problem which, like that of haemin, taxed the ingenuity of many investigators. Not so long ago our knowledge of the chlorophyll structure was so fragmentary and disconnected that the very name of the compound was omitted from standard textbooks. But since then the substance has

[1] Fischer and Reinecke, *Z. physiol. Chem.*, 1939, **258**, 9.

* Note.—A large number of compounds related to bilirubin have been studied, and for an account of these the reader is recommended to consult *Die Chemie des Pyrolls*, by Fischer and Orth.

been submitted to rigorous scrutiny, its reactions have been classified, its decomposition products brought into relation with each other, and a number of syntheses of derivatives accomplished, so that the information now at our disposal is sufficient to render a coherent account of it possible.[1]

A study of the literature on chlorophyll is beset with difficulties. The nomenclature of the subject is to a large extent new and different from that with which the organic chemist is familiar; for instead of referring to acids in the usual terms, the investigators have christened them with a brand-new set of names, and as these titles have established themselves in the literature, it is hopeless to expect that they will be altered now.

At the present time the derivatives of *chlorophyll* having the magnesium atom in the molecule are called *chlorophyllides*. The derivatives from which the magnesium atom has been eliminated and which still retain the two extra hydrogen atom attached to a pyrrol nucleus, the vinyl group at carbon atom 2 of pyrrol nucleus I., and also have intact the carbocyclic ring between carbon atoms 6 and γ are known as *phorbides* or *phorbins*. If derived from *chlorophyll-a* the compound is a *phorbide-a*. If *chlorophyll- b* is the parent substance the derivature is a *phorbide- b*. Next in complexity are the *chlorins* from *chlorophyll-a*. In these derivatives the "extra" hydrogen atoms and the vinyl group are still in the molecule, but the carbocyclic ring is open between carbon atoms 9 and 10. The corresponding derivatives from *chlorophyll-b* are the *rhodins*. The *purpurins* like the *chlorins* and *rhodins* have the "extra" hydrogen atoms and the vinyl group in the molecule, but are oxidized at carbon atom 10. When the vinyl group of any of these compounds has been reduced to an ethyl group the name of the compound is prefixed by *meso*.

When a chlorophyll compound loses the two "extra" hydrogen atoms it becomes a *porphyrin*. If the carbocyclic ring is intact the prefix *phaeo-* is used. The porphyrins derived from the chlorins and retaining some or all of the carbon atoms attached to carbon atoms 6 and γ are known as *chloroporphyrins*. Inspection of the names and formulae in the following sections will make the meanings of these terms clearer.

[1] For a general account of Willstätter's researches see, *Ber.*, 1914, **47**, 2831; Willstätter and Stoll, *Untersuchungen über Chlorophyll*, Berlin 1913, and for an account of more recent work, see Fischer, *J.*, 1934, 245.

Chlorophyll contains within its molecule a complex and sensitive grouping capable of undergoing various intramolecular changes under the action of reagents; and these rearrangements formed one of the most puzzling factors in the problem.

The extraction of chlorophyll from plants is a simple operation. The leaves are removed from their stems, dried and powdered. Alcohol is then poured over the powder and the mixture kept constantly stirred. After a time the chlorophyll passes into the liquid, from which it can be extracted. By this process a " crystalline chlorophyll " is obtained; whereas when ether or acetone-water is substituted for alcohol, an " amorphous chlorophyll " is found in solution.[1]

The composition of " amorphous chlorophyll " may be regarded provisionally as corresponding to $C_{55}H_{72}N_4O_5Mg$.

The complication of the formula makes it obvious that our chief knowledge of chlorophyll must be gained through an acquaintance with its degradation products. Three main types of reaction might be employed to break down the chlorophyll molecule: oxidation, reduction, and hydrolysis. In practice, it has been found that most information is gained from a study of the last class; for oxidation and reduction proved to be comparatively useless in so far as the production of immediate decomposition products is concerned.

Along with chlorophyll, two other colouring matters are found in leaves. The one, carotene, is coppery in colour and is identical with the substance which gives their colour to carrots. It is a hydrocarbon of the composition $C_{40}H_{56}$.* The other colouring material, xanthophyll, is dark brown-red in tint; has the composition $C_{40}H_{56}O_2$; and is an oxidation product of carotene.[2] It is suggested that in summer the green of chlorophyll masks the tints of carotene and xanthophyll; but when in autumn the chlorophyll decays, the reddish pigments become visible and give the leaves their autumn colouring.

It is interesting to note that the chlorophyll of brown algae is identical with that derived from land-plants,[3] a fact which appears most unexpected from the tints of the organisms.

As has been pointed out already, the extraction of chlorophyll from plants by means of ether yields an amorphous substance.

[1] Willstätter and Benz, *Annalen*, 1908, **358**, 267; Willstätter and Oppé, *ibid.*, 1911, **378**, 1.

* See Chapter II.

[2] Willstätter and Mieg. *Annalen*, 1907, **355**, 1; Kuhn, Winterstein, and Lederer, *Z. physiol. Chem.*, 1931, **197**, 141.

[3] Willstätter and Page, *Annalen*, 1914, **404**, 237.

Specimens of this amorphous product were obtained, under carefully regulated conditions, from about two hundred different kinds of plants; and, on examination, it was found that all the samples yielded on decomposition approximately the same amount—about 30 per cent.—of an alcohol named phytol.[1] This at once suggests that amorphous chlorophyll may be the phytyl ester of some acid.

The case of "crystalline chlorophyll" must now be examined. It also is found to be a di-ester: but instead of the phytyl radicle it contains an ethyl group; the second carboxy radicle is esterified with methyl alcohol. Thus, during the extraction of chlorophyll with alcohol, it is clear that the phytyl group has been replaced by an ethyl radicle. This process is traced to the action of an enzyme, chlorophyllase, which is found in plants. During prolonged processes of maceration with alcohol, the chlorophyllase from the plant tissues substitutes ethyl for phytyl alcohol, and "crystalline chlorophyll" is the result.[2]

Reference to the formulae in diagram I. shows this relationship and others between chlorophyll-*a* and its derivatives.

Diagram I.

[1] Willstätter, Hocheder, and Hug, *Annalen*, 1909, **371**, 1; Willstätter and Oppé, *Annalen*, 1911, **378**, 1.

[2] Willstätter and Stoll, *Annalen*, 1910, **378**, 18.

2. *Chlorophyll-a and Chlorophyll-b*

Half a century ago Stokes [1] proved that the chlorophyll occurring in plants is a mixture of two substances differing in their spectra and solubilities in certain solvents; but his paper remained almost unnoticed by later workers, and it was not until 1912 that definite chemical corroboration of his statements was obtained.[2]

The newer researches on the subject started from a different standpoint. When chlorophyll was treated with certain reagents, it was found that it yielded a mixture of two substances: chlorin-*e* and rhodin-*g*. These compounds are found to occur among the degradation products of chlorophyll in the almost constant proportion of five molecules of chlorin-*e* to two molecules of rhodin-*g*. At first sight it appears easy to account for this by assuming that the chlorophyll skeleton contains five chlorin nuclei and two rhodin nuclei; so that in its decomposition it could give rise to the products in the required proportions. This explanation breaks down at once, however, when it is shown that the molecular weights of chlorin and rhodin are each approximately the same as that of chlorophyll itself, if we deduct from the latter the molecular weight of the phytyl radicle which does not occur in either the chlorin or the rhodin molecule. Clearly, if the molecular weight of chlorin-*e* is nearly the same as that of the non-phytyl part of the chlorophyll molecule, there is no room in the latter substance for five chlorin nuclei.

Evidently only one way can be found out of the difficulty. It is necessary to assume that chlorophyll is a mixture of two components, one of which on degradation produces chlorin-*e* whilst the other gives rise to rhodin-*g*. This view has actually been proved correct [3] by the separation of chlorophyll into two portions: chlorophyll-*a* and chlorophyll-*b*. By shaking a solution of chlorophyll in petroleum ether, with some water containing methyl alcohol, it is found that chlorophyll-*a* remains in the petroleum ether whilst the chlorophyll-*b* passes into the aqueous layer.

Chlorophyll-*a* is a bluish-black in tint, contains half a molecule of water of crystallization, and gives only chlorin-*e*

[1] Stokes, *Proc. Roy. Soc.*, 1864, **13**, 144; compare Tswett, *Zeit. Biol.*, 1907, 5, 6; *Ber. deutsch. bot. Ges.*, 1906, **24**, 316; 1907, **25**, 137; *Ber.*, **41**, 1352.

[2] Willstätter and Isler, *Annalen*, 1912, **390**, 269.

[3] *Ibid.*

when it is decomposed. Chlorophyll-*b* is greenish-black in colour; its crystals are anhydrous; and when it is broken down it yields only rhodin-*g*. On analysis, chlorophyll-*a* is found to be:

$$[C_{32}H_{30}ON_4Mg](COOCH_3)(COOC_{20}H_{39}) + \frac{1}{2}H_2O$$

whilst chlorophyll-*b* gives results corresponding to:

$$[C_{32}H_{28}O_2N_4Mg](COOCH_3)(COOC_{20}H_{39})$$

When the chlorophylls themselves are not required it is more convenient to hydrolyse amorphous chlorophyll to the phaeophorbides-*a* and -*b*, and separate those from ethereal solution by extraction with hydrochloric acid of different strengths. This method of separation depends for its successful operation on the differences in basicity of the components of the mixture. It cannot, however, be applied to the chlorophylls and their derivatives containing a labile magnesium atom in the molecule.[1]

3. *The Magnesium Atom in the Chlorophyll Molecule*

The part played by the magnesium atom in the structure of chlorophyll cannot be ignored if a true picture of the substance is to be obtained; yet it must be admitted that in some respects the problem which it presents is a thorny one.

From the fact that the magnesium atom remains as part of the structure of aetiophyllin, $C_{31}H_{34}N_4Mg$, it is clear that the metal must be attached to carbon or nitrogen; since all the oxygen has disappeared in the process of degradation to which the original chlorophyll has been submitted.

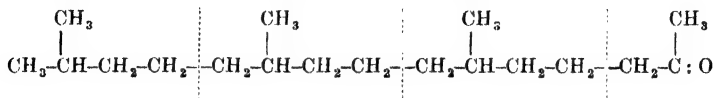
Now in all the magnesium-carbon compounds with which we are acquainted, the magnesium is easily removed by the action of water; it certainly cannot withstand the attack of alkali. Further, the nitrogen-magnesium bond also appears to be a weak one, if we may judge from the behaviour of magnesium methyl iodide with pyrrol.[2] Clearly the affinity which holds the magnesium atom to the chlorophyll nucleus is no ordinary bond; and we are left to conjecture its nature.

[1] Willstätter and Stoll, *Chlorophyll*, 236.
[2] Hess and Wissing, *Ber.*, 1914, **47**, 1416.

Willstätter [1] regards the metallic atom as forming a complex with the basic groups of the molecule.

4. *The Phytyl Group of Chlorophyll*

By the action of alkali or by enzyme action in the presence of alcohol chlorophyll splits off a molecule of the alcohol, phytol, $C_{20}H_{39}OH$. Phytol can be catalytically reduced to a saturated alcohol, $C_{20}H_{41}OH$, indicating the presence of an ethylenic bond in the molecule. Phytol forms an ozonide, which can be broken down to yield glycollic aldehyde, $CH_2OH—CHO$ and a ketone $C_{18}H_{36}O$. The ethylenic bond of phytol is therefore in the 2 : 3-position relative to the hydroxyl group. On the assumption that phytol is built up from reduced isoprene units a possible structure for the ketone, $C_{18}H_{36}O$ would be,

$$CH_3-\overset{\overset{CH_3}{|}}{C}H-CH_2-CH_2- \vdots -CH_2-\overset{\overset{CH_3}{|}}{C}H-CH_2-CH_2- \vdots -CH_2-\overset{\overset{CH_3}{|}}{C}H-CH_2-CH_2- \vdots -CH_2-\overset{\overset{CH_3}{|}}{C}:O$$

This assumption was proved to be correct by the synthesis of a compound of this structure, which was found to be identical in properties with the ketone derived from phytol.[2]

The starting point in the synthesis of the ketone was farnesol. This compound was converted into its acetate (I.) and reduced in the presence of palladized calcium carbonate to the saturated alcohol, hexahydrofarnesol (II.). Catalytic reduction of farnesol itself was not satisfactory as the main product was the completely reduced substance, farnesane. Phosphorus tribromide converted hexahydrofarnesol into the corresponding bromide, which on interaction with ethyl sodioacetoacetate yielded the acetoacetate derivative (III.). Hydrolysis of this substance afforded the ketone, $C_{18}H_{36}O$ (IV.). The structural changes are :

[1] Willstätter and Pfannenstiel, *Annalen*, 1908, **358**, 215; Willstätter and Fritzsche, *Annalen*, 1910, **371**, 46.

[2] Willstätter, Mayer, and Hüni, *Annalen*, 1910, **378**, 73; Willstätter, Schuppli, and Mayer, *ibid.*, 1919, **418**, 121; Fischer and Löwenberg, *ibid.*, 1928, **464**, 69.

$$CH_3\text{-}\overset{\overset{CH_3}{|}}{C}{=}CH\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{C}{=}CH\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{C}{=}CH\text{-}CH_2O.CO.CH_3 \qquad (I.)$$

$$\Big\downarrow \text{ catalytic reduction}$$

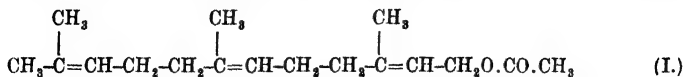
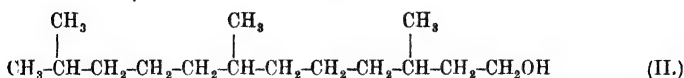
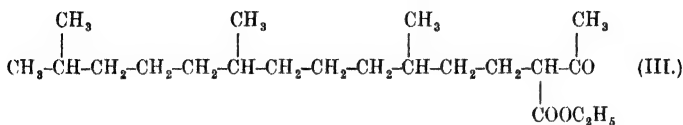
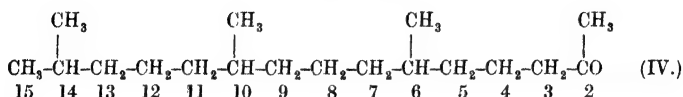
$$CH_3\text{-}\overset{\overset{CH_3}{|}}{CH}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{CH}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{CH}\text{-}CH_2\text{-}CH_2OH \qquad (II.)$$

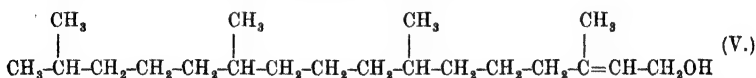
$$\Big\downarrow \; (1)\ P.Br_3 \quad (2)\ CH_3\text{—}CO.\underset{\underset{Na}{|}}{CH}.COOC_2H_5$$

$$CH_3\text{-}\overset{\overset{CH_3}{|}}{CH}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{CH}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{CH}\text{-}CH_2\text{-}CH_2\text{-}\underset{\underset{COOC_2H_5}{|}}{CH}\text{-}\overset{\overset{CH_3}{|}}{CO} \qquad (III.)$$

$$\Big\downarrow \text{ Hydrolysis}$$

$$CH_3\text{-}\overset{\overset{CH_3}{|}}{CH}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{CH}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{CH}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{CO} \qquad (IV.)$$

15 14 13 12 11 10 9 8 7 6 5 4 3 2

By piecing this structure and that of glycollic aldehyde together the structure (V.) is suggested for phytol.

$$CH_3\text{-}\overset{\overset{CH_3}{|}}{CH}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{CH}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{CH}\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{C}{=}CH\text{-}CH_2OH \qquad (V.)$$

The synthesis of phytol itself from the ketone, $C_{18}H_{36}O$ (IV.) fully confirmed this structure. These final steps in the synthesis of phytol are shown below.

The ketone, $C_{18}H_{36}O$, 6 : 10 : 14-trimethylpentadecan-2-one (IV.) was condensed with acetylene by the aid of sodamide to give the unsaturated alcohol (VI). This acetylene derivative was reduced with hydrogen and palladized calcium carbonate to the corresponding ethylene derivative (VII.) which by the influence of acetic anhydride underwent intramolecular re-arrangement to the alcohol, 3 : 7 : 11 : 15-tetramethyl-Δ^2-hexadecen-1-ol (VIII.) identical in its properties with phytol isolated from chlorophyll.[1]

[1] Fischer and Löwenberg; *Annalen*, 1929, **475**, 183; Heilbron and Thompson, *J.*, 1929, 883.

$$CH_3-\overset{CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\overset{CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\overset{CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\overset{CH_3}{\overset{|}{\underset{\underset{O}{\|}}{C}}} \qquad (IV.)$$

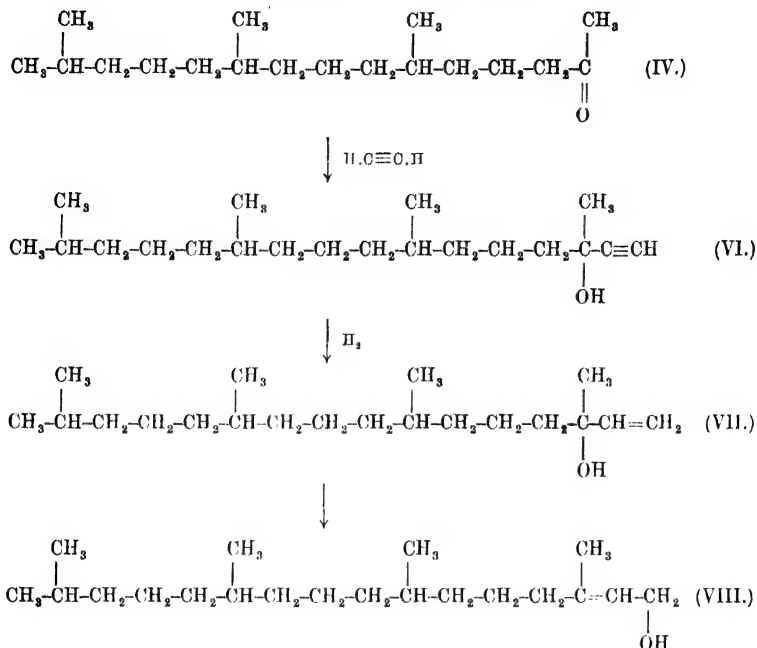
$$\downarrow H.C{\equiv}C.H$$

$$CH_3-\overset{CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\overset{CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\overset{CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\overset{CH_3}{\overset{|}{\underset{\underset{OH}{|}}{C}}}-C{\equiv}CH \qquad (VI.)$$

$$\downarrow H_2$$

$$CH_3-\overset{CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\overset{CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\overset{CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\overset{CH_3}{\overset{|}{\underset{\underset{OH}{|}}{C}}}-CH{=}CH_2 \qquad (VII.)$$

$$\downarrow$$

$$CH_3-\overset{CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\overset{CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\overset{CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\overset{CH_3}{\overset{|}{C}}{=}CH-\underset{\underset{OH}{|}}{CH_2} \qquad (VIII.)$$

5. *The Pyrrole Degradation Products*

By the action of hydrated oxalic acid in alcoholic solution, the magnesium atom of chlorophyll may be replaced by two hydrogen atoms. The new compound phytyl phaeophorbide (phaeophytin) on treatment for a short time with methyl alcoholic potassium hydroxide loses its phytyl and methyl groups by hydrolysis, and at the same time adds on one molecule of water to yield the tribasic acid chlorin-*e*, $C_{31}H_{33}N_4(COOH)_3$. Chlorin-*e* will be dealt with more fully in a later section. For our present purpose it is sufficient to note that the considerable decrease in molecular carbon content in passing from chlorophyll to chlorin-*e* is due to the hydrolysis of two ester side chains, while the central portion of the molecule, bearing the four nitrogen atoms, remains substantially intact. It will also be shown later that the production of a third carboxyl group in chlorin-*e* does not entail any deep-seated change in the central system of pyrrole nuclei. Chlorin-*e* when oxidized with chromic acid is broken down to yield haematic acid (I.) and methyl ethylmaleinimide (II.).

On reduction with hydrogen iodide and acetic acid chlorin-*e* is degraded, giving haemopyrrole (III.) and phyllopyrrole (IV.).[1] Another chlorophyll degradation product, phylloporphyrin, $C_{31}H_{35}N_4$. COOH also yields these simple pyrroles on oxidation and reduction, as well as cryptopyrrole (V.) and β-citraconic anhydridepropionic acid (VI.). If phylloporphyrin be first brominated and then oxidized bromocitraconimide (VII.) is produced. The molecular composition of chlorophyll and these experimental facts point to the presence of four pyrrole nuclei in the molecule. It may also be concluded that some, if not all, of the nuclei carry methyl groups in the β-position, that one nucleus carries a propionic acid group, and that ethyl groups or groups capable of reduction to this radicle are also present in the β-positions of two nuclei. The appearance of methyl groups in the α-position of the pyrrole degradation products is taken as evidence that the four nuclei are linked up with one another by carbon atoms at these points to form a large cyclic arrangement such as (VIII.). The following scheme shows the structures of the pyrrole degradation products and their sources. The molecular formulae of chlorophyll-*a* and its derivatives are given.

[1] Willstätter and Asahina, *Annalen*, 1910, **373**, 227; 1911, 385, 188.

Chlorophyll a
hydrated oxalic acid
Phytyl phaeophorbide a
KOH
Chlorin-e
HI
CH_3COOH
chromic acid
Phylloporphyrin
Br_2 + chromic acid
(I)
(II)
(III)
(IV)
(V)
(VI)
(VII)
(VIII)

6. *The Porphyrin Degradation Products*

Chlorophyll on alkaline degradation yields various porphyrins. Of these the most important are pyrroporphyrin, $C_{30}H_{33}N_4 . COOH$, phylloporphyrin, $C_{31}H_{35}N_4 . COOH$ and rhodoporphyrin, $C_{30}H_{32}N_4 (COOH)_2$.[1] Both phylloporphyrin and rhodoporphyrin can be converted into pyrroporphyrin, the former losing a methylene group by the action of sodium ethoxide and the latter losing carbon dioxide on being heated. The action of heat on pyrroporphyrin itself decarboxylates it yielding pyrroactioporphyrn, $C_{30}H_{34}N_4$. The relationship between the four compounds is obviously a close one, phylloporphyrin being a methylpyrroporphyrin and rhodoporphyrin a carboxy-derivative of pyrroporphyrin. The three first-mentioned porphyrins were at one time thought to be fully substituted tetramethyl - triethyl - porphyrinpropionic acids. It was discovered, however, that pyrroporphyrin and phylloporphyrin (but not rhodoporphyrin), on bromination followed by oxidation yielded bromo-citraconimide. This pointed clearly to the presence of a hydrogen atom at the β-position in a pyrrole nucleus of the two porphyrins.[2]

The presence of a hydrogen atom in one pyrrole nucleus of pyrroporphyrin was confirmed by its conversion into 1 : 3 : 5 : 8-tetramethyl-2 : 4 : 6-triethlyporphyrin-7-propionic acid ("porphinmonopropionic acid III."). This conversion was accomplished by use of the method found so successful in the transformation of deuteroporphyrin into haematoporphyrin.* The nuclear hydrogen atom of pyrroporphyrin was replaced by an acetyl group, and the acetyl-compound reduced to the carbinol, which yielded the ethyl-derivative on further reduction.[3] This ethylpyrroporphyrin was found to be identical with "porphinmonopropionic acid III." (III.), the structure of which was known from its synthesis from the two methenes (I.) and (II.).

[1] Hoppé-Seyler, *Z. physiol. Chem.*, 1879, **3**, 339; 1880, **4**, 193; Schunck, *Proc. Roy. Soc.*, 1891, **50**, 302; Schinck and Marchleswki, *Proc. Roy. Soc.*, 1895, **57**, 314; *ibid.*, *Annalen*, 1894, **284**, 81; Willstätter and Fritzsche, *Annalen*, 1909, **371**, 33.

[2] Fischer and Triebs, *Annalen*, 1928, **466**, 188.

* See p. 129.

[3] Fischer, Weichmann, and Zeile, *Annalen*, 1929, **475**, 241.

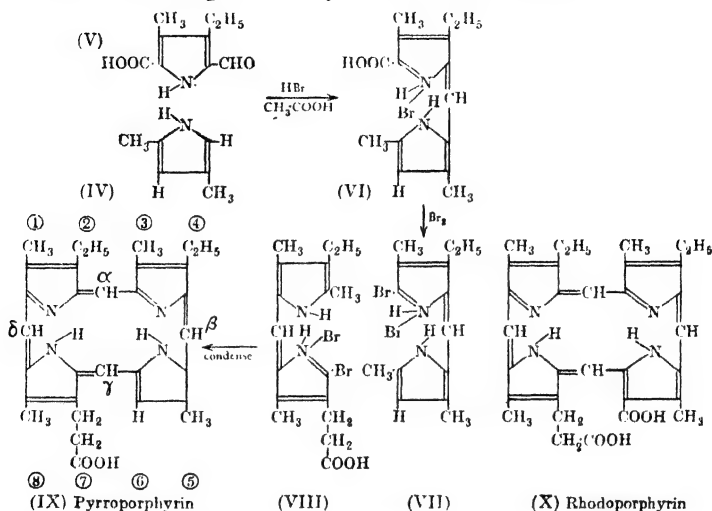
(I) (II) (III)

Pyrroporphyrin must therefore have one of the three following structures, as each would yield "porphinmonopropionic acid III." on the introduction of an ethyl group into the molecule.

The synthesis of pyrroporphyrin by two different routes showed conclusively that the structure with the nuclear hydrogen atom at position 6 was the correct one. One of the syntheses was by a direct method, the other was through rhodoporphyrin. The direct synthesis had for its starting point 2 : 4-dimethylpyrrole (IV.) and 2-aldehydo-4-methyl-3-ethylpyrrole-5-carboxylic acid (V.). These were condensed by means of a mixture of acetic and hydrobromic acids to yield the methene hydrobromide (VI.). By the action of bromine in acetic acid the carboxyl group of the methene was replaced by bromine. This bromomethene (VII.) and 5′-bromo-3 : 5 : 3′-trimethyl-4-ethyl-4′-β-carboxyethylpyrromethene hydrobromide (VIII.) on fusion with a mixture of succinic and methylsuccinic acids were converted into a mixture of four porphyrins which included bromopyrroporphyrin and pyrroporphyrin

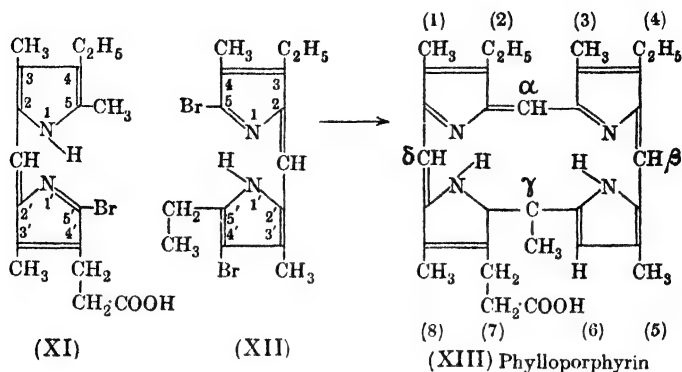
(IX.). The latter was identical with pyrroporphyrin from natural sources.[1] The steps in the synthesis are as follows :

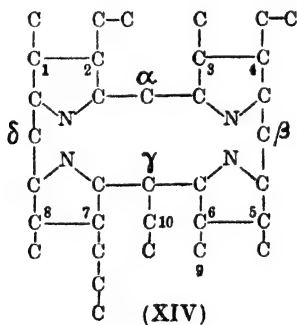
(V) (IV) (VI)

(IX) Pyrroporphyrin (VIII) (VII) (X) Rhodoporphyrin

Rhodoporphyrin, which contains two carboxyl groups and readily loses one of them passing into pyrroporphyrin, and does not yield bromocitraconimide on bromination and oxidation, is concluded to be 6-carboxypyrroporphyrin (X.). This structure is supported by the fact that the propionic acid group in the porphyrins only splits off carbon dioxide with difficulty. On the other hand, phylloporphyrin on bromination and oxidation, like pyrroporphyrin, yields bromocitraconimide. In phylloporphyrin, therefore, position 6 carries a hydrogen atom and the additional methyl group is attached to one of the four " bridge " carbon atoms. All four isomers have been synthesized, and the compound with the methyl group attached to the γ-carbon atom shown to be identical with phylloporphyrin obtained from chlorophyll. The synthetic phylloporphyrin (XIII.) was prepared from the hydrobromides of 5′-bromo-3 : 5 : 3′-trimethyl-4-ethyl-4′-β-carboxyethylpyrromethene (XI.) and 5 : 4′-dibromo-4 : 3′-dimethyl-3 : 5′-diethylpyrromethene (XII.).[2] The structures of these compounds are shown below.

[1] Fischer, Berg, and Schormüller, *Annalen*, 1929, **473**, 211 ; 1930, **480**, 109, 189 ; 1930, **482**, 232.

[2] Fischer and Helberger, *Annalen*, 1930, **480**, 235 ; Fischer, Siedel, and Le Thierry d'Ennequin, *ibid.*, 1933, **500**, 137.

(XI) (XII) (XIII) Phylloporphyrin

The proofs that rhodoporphyrin has a carboxyl group at position 6, and that phylloporphyrin carries a methyl group at the γ-bridge carbon atom are important as they permit a further elaboration of the skeleton to be made; and allowing for the phytyl and methyl ester groups of chlorophyll all but one of the carbon atoms are accounted for. The missing carbon atom may be assumed to be attached to carbon atom 10. The partial chlorophyll skeleton may, therefore, be written down as (XIV.)

(XIV)

In concluding this section it must be pointed out that the conversion of chlorophyll into porphyrins takes place by the action of sodium ethoxide at a high temperature in a sealed tube, or by the action of alkali at 200–240° C. followed by treatment with acid. These are drastic conditions and secondary syntheses are possible. The presence of the porphyrin ring in chlorophyll and its near derivatives, therefore, cannot be regarded as fully

established by these changes. The structural relationship must, however, be a close one as haemin porphyrins can be converted into chlorins and rhodins, and pyrroporphyrin into mesoporphryin obtained from haemin.[1] A further confirmation of the relationship between the two classes of compounds is the conversion of chlorophyll derivatives into porphyrins by bacterial action.[2]

7. *The Phaeo- and Chloro-porphyrins*

Reference to the introductory diagram on page 137 shows that phaeophorbide-*a* is obtained from chlorophyll-*a* by elimination of a magnesium atom and the phytyl group, and their replacement by hydrogen atoms. These changes are brought about by the action of oxalic acid in alcoholic solution followed by acid hydrolysis, and take place without secondary decompositions.[3]

Phaeophorbide-*a* contains a free carboxyl group and the original methyl ester grouping of chlorophyll, which resists hydrolysis under conditions which separate phytyl alcohol. The formula may be written as $\left(C_{32}H_{32}ON_4\right)\begin{matrix}-COOCH_3\\-COOH\end{matrix}$. If mild reagents convert phaeophorbide-*a* into porphyrins it may be concluded that no secondary changes take place and that the porphyrin structure is present in phaeophorbide-*a* and consequently in chlorophyll. Hydriodic acid in glacial acetic acid at temperatures no higher than 50–60° C. followed by atmospheric oxidation converts phaeophorbide-*a* (VII.) into phaeoporphyrin-*a* 5 (VI.). The latter compound is isomeric with phaeophorbide-*a*, and loses its methyl ester grouping by the further action of hydriodic acid, being converted into phylloerythrin (II.). This compound like phaeoporphyrin-*a* 5 contains a carboxyl group and a carbonyl group. Phylloerythrin is a vital degradation product of chlorophyll, and has been isolated from such sources as the bile and faeces of herb-eating animals.[4]

[1] Fischer, Treibs, and Helberger, *Annalen*, 1928, **466**, 243 ; 1929, **471**, 285 ; Fischer, Helberger, Platz, and Niemer, *ibid.*, 1930, **479**, 27 ; Fischer, Gebhardt, and Rothaas, *ibid.*, 1930, **482**, 1 ; Fischer and Riedl, *ibid.*, 1931, **486**, 178.

[2] Fischer and Hendschel, *Z. physiol. Chem.*, 1931, **198**, 33 ; 1933, **222**, 250.

[3] Fischer et al., *Annalen*, 1929, **474**, 65 ; 1930, **478**, 54, 284 ; **480**, 197 ; **482**, 225.

[4] Marchlewski, *Z. physiol. Chem.*, 1929, **185**, 8 ; Fischer and Hess, *ibid.*, 1930, **187**, 133.

Phylloerythrin yields pyrro-, phyllo- and rhodoporphyrins on treatment with sodium ethoxide in the presence of air, and on reduction is converted into deoxophylloerythrin (III.).[1] Both phylloerythrin and its reduction product, deoxophylloerythrin, have been prepared from porphryins of known structure, the former from the dimethyl ester of chloroporphyrin-*e* 4 (I.), and the latter from phylloporphyrin (V.).[2] Diagram II shows these changes in tabular form.

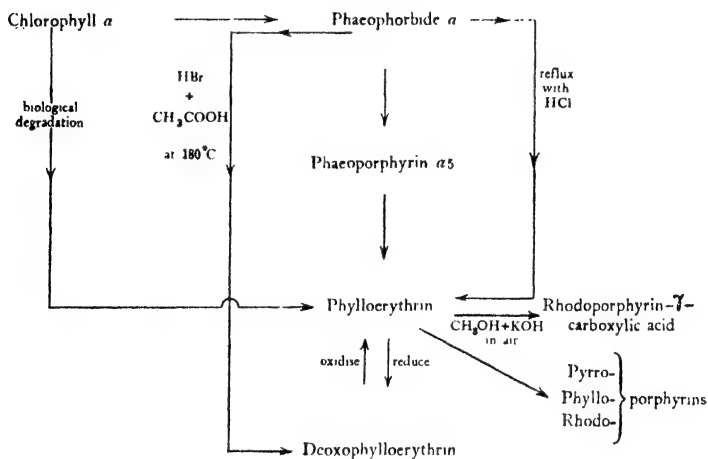



DIAGRAM II.

The structural interpretations of the conversions of the porphyrins into the erythrins are given below, and considered in conjunction with the production of phylloporphyrin (V.) and rhodoporphyrin from phylloerythrin, leave very little doubt about the structure of the last-named substance.

[1] Fischer, Moldenhauer and Süs, *Annalen*, 1931, **485**, 1; 1931, **486**, 107.

[2] Fischer, Müller, and Leschhorn, *Annalen*, 1936, **523**, 164; Fischer, Speitmann and Meth, *Annalen*, 1934, **508**, 154.

C_2H_5ONa →

(I) Chloroporphyrin e_4 dimethyl ester

(II) Phylloerythrin

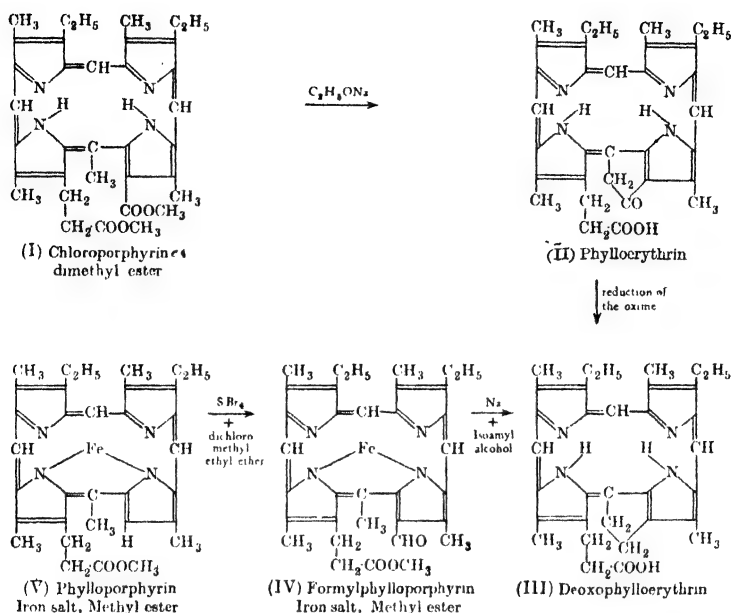
↓ reduction of the oxime

(V) Phylloporphyrin Iron salt, Methyl ester

← SBr_4 + dichloro methyl ethyl ether

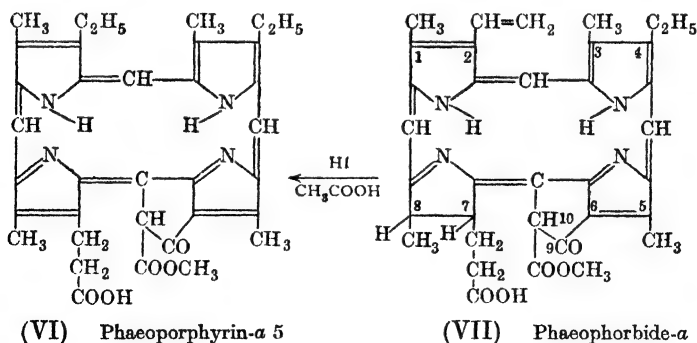
(IV) Formylphylloporphyrin Iron salt, Methyl ester

← Na + Isoamyl alcohol

(III) Deoxophylloerythrin

The structure of phylloerythrin having been established it is now possible to give a structure to phaeoporphyrin-*a* 5 as a β-ketonic ester (VI.). Phaeophorbide-*a* (VII.) will contain the same system but differing from phaeoporphyrin-*a* 5 in some details.

← HI, CH_3COOH

(VI) Phaeoporphyrin-*a* 5

(VII) Phaeophorbide-*a*

Phaeoporphyrin-*a* 5 is here shown with the methyl ester grouping attached to the carbocyclic ring at carbon atom 10, and not as a methyl propionate at carbon atom 7. This carbomethoxy group has come through the chemical changes intact

from phaeophorbide-*a* and is also present in chlorophyll *a*. It is, therefore, important to know that it and, consequently, the phytyl group of chlorophyll are correctly placed. This problem was approached from two different directions. It was found that phaeophorbide-*a* like other phorbides and chlorins, when heated in dilute diphenyl solution to 180–250° C. lost a carbomethoxy group and was converted into pyrophaeophorbide-*a*.

Pyrophaeophorbide-*a* contains a free carboxyl group, and it is therefore, probable that the decomposition of phaeophorbide-*a* takes place at some point other than at its free carboxyl group. As phaeophorbide-*a* yields, either directly or indirectly, different porphyrins such as phaeoporphyrin-*a* 5 and pyrroporphyrin, known to contain the propionic acid grouping

$$—CH_2—CH_2—COOH$$

it is concluded that this acid grouping survives the change from phaeophorbide-*a* into its pyro-derivative and is the one which carries the phytyl group of chlorophyll.[1] The second line of approach leads to the same conclusion. Ethyl chlorophyllide prepared from chlorophyll by the action of ethyl alcohol contains an ethyl radicle in place of a phytyl group. It is converted into the ethyl ester of phaeoporphyrin-*a* 5 (VIII.) by the action of hydriodic acid. The porphyrin in its turn is converted into the ethyl ester of phylloerythrin (IX.). The phytyl group of the original chlorophyll must have been attached at the propionic acid side chain, which in ethyl chlorophyllide, phaeoporphyrin-*a* 5 ester and phylloerythrin ester carries the ethyl group.[2] The methyl ester grouping is therefore at carbon atom 10 in phaeoporphyrin-*a* 5 and chlorophyll. See page 153.

When phaeophorbide-*a* was hydrolysed by hot methyl-alcoholic caustic potash for a short time out of contact with atmospheric oxygen it was converted into chlorin-*e*, $C_{34}H_{36}O_6N_4$, which has been shown by salt and ester formation to be a tribasic acid. The transformation, therefore, consists of the hydrolysis of the ester grouping of phaeophorbide-*a* and the production of a new carboxyl group by the addition of one molecule of water.[3] The fission of the carbocyclic ring between carbon atoms 9 and 10

[1] Conant and Hyde, *J. Amer. Chem. Soc.*, 1929, **51**, 3668.

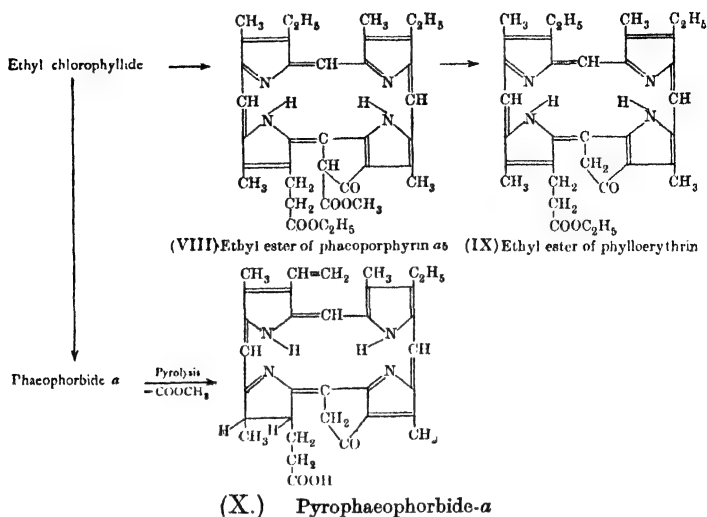
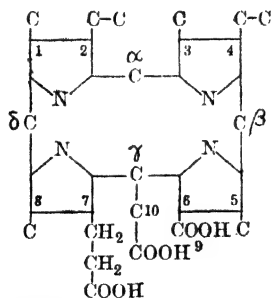
[2] Fischer, Süs, and Clebs, *Annalen*, 1931, **490**, 38; 1933, **506**, 107.

[3] Willstätter and Utzinger, *Annalen*, 1911, **382**, 171; Fischer and Moldenhauer, *ibid.*, 1938, **478**, 54; Treibs and Wiedemann, *ibid.*, 1928, **466**, 264; 1929, **471**, 146.

Ethyl chlorophyllide →

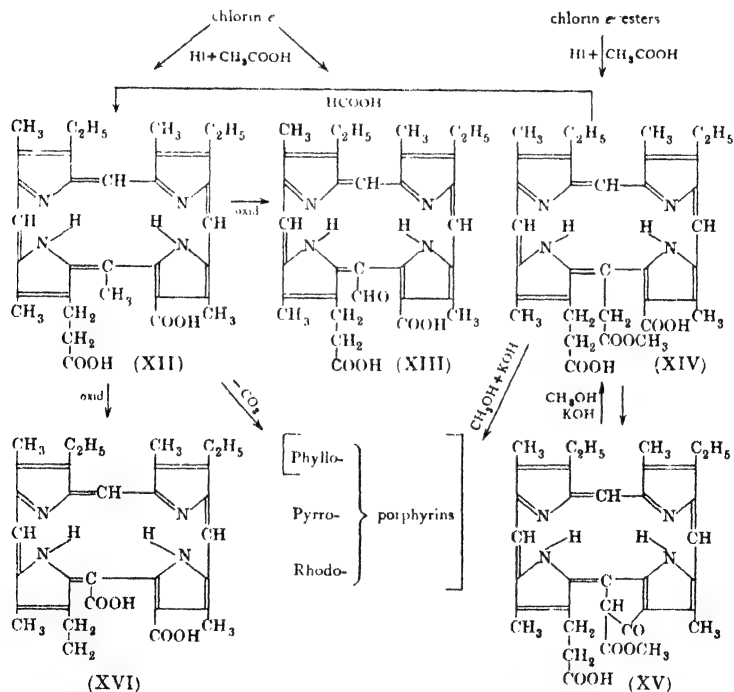
(VIII) Ethyl ester of phaeoporphyrin *a*5 → (IX) Ethyl ester of phylloerythrin

Phaeophorbide *a* —Pyrolysis, $-COOCH_3$→

(X.) Pyrophaeophorbide-*a*

(XI.) affords a ready explanation of the formation of a new carboxyl group at carbon atom 6. This is supported by the fact that phaeoporphyrin-*a* 5 on hydrolysis with cold alcoholic potassium hydroxide is converted into chloroporphyrin-*e* 6 (XIV.) which can be reconverted to phaeoporphyrin-*a* 5. The skeleton structure of chlorin-*e* may be written down provisionally as (XI.).

(XI.) Chlorin-*e* skeleton.

Chlorin-*e*, like phaeophorbide-*a*, yields porphyrins by the action of hydriodic and acetic acids. Two principal chloroporphyrins, *e* 4, $C_{33}H_{36}O_4N_4$ and *e* 5, $C_{33}H_{34}O_5N_4$ have been isolated in this way from chlorin-*e*, and a third, *e* 6, $C_{35}H_{38}O_6N_4$ obtained by the same reagents from chlorin-*e* di- and tri-methyl

esters, and from phaeoporphyrin-*a* 5 by hydrolytic fission. Chloroporphyrin-*e* 6 (XIV.) by the action of formic acid loses a methyl ester grouping to yield chloroporphyrin-*e* 4 (XII.), which in its turn can be converted into phylloporphyrin by decarboxylation and into rhodoporphyrin-γ-carboxylic acid (XVI.) by oxidation. Chloroporphyrin-*e* 4 may also be readily oxidized to chloroporphyrin-*e* 5 (XIII.). This ease of oxidation of the γ-methyl group is accounted for by the presence of the carboxyl group at position 6.

Decomposition of chloroporphyrin-*e* 6 directly by the action of methyl-alcoholic potassium hydroxide also leads to the formation of the simpler compounds, pyrro-, phyllo- and rhodoporphyrins. From these relationships the three chloroporphyrins may be formulated as shown below.

If these conclusions regarding the structures of the chloroporphyrins-*e* 4, *e* 5 and *e* 6 are correct the compounds respectively are the γ-methyl, γ-formyl and γ-methylacetate-derivatives of rhodoporphyrin.

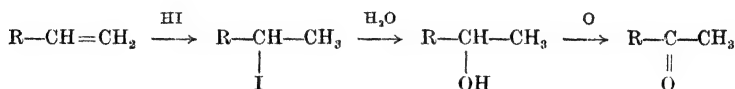
8. *The Phaeophorbides and Chlorins*

These are the green derivatives of chlorophyll. In the previous section their close relationship to their porphyrins has been shown. They differ in some important respects from the porphyrins and in this section these differences in structure will be dealt with.

To distinguish the chlorophylls, the phorbides and the chlorins from their porphyrins they are referred to as *iso*porphyrins. The *iso*porphyrins, but not their porphyrins, take part in the "oxo-reaction." This change is brought about by the action of cold hydriodic and acetic acids in the presence of oxygen, and is, in effect, the oxidation of a vinyl group to an acetyl group.[1] When phaeophorbide-*a* was treated in this way the product was oxophaeoporphyrin-*a* 5 (I.), which was shown to contain two carbonyl groups by the production of a dioxime. An acetyl group could, however, arise by oxidation from either an ethylidene $=CH—CH_3$, or a vinyl group, $—CH=CH_2$. This point was cleared up by comparing the behaviour of protoporphyrin (II.), which is known to contain two vinyl groups with that of methyl phaeophorbide-*a* (III.), when each was allowed to react with diazoacetic ester.[2] The dimethyl ester of protoporphyrin reacted with two molecules of methyl diazoacetate. The compound (IV.) formed broke down on oxidation into haematic acid and methylmaleinimide*cyclo*propane carboxylic acid (VI.). Methyl phaeophorbide-*a* (III.) reacted with one molecule of the diazoacetic ester. The product (V.) formed was converted into a porphyrin derivative, which also yielded the maleinimide derivative (VI.). Other phorbides and chlorins reacted with methyl diazoacetate, but their porphyrin derivatives, such as phaeoporphyrin-*a* 5 and phylloerythrin, did not. Comparison of the absorption spectra of the diazoacetic ester derivatives of protoporphyrin and methyl phaeophorbide-*a* showed parallel changes from the spectra of the parent substances. Phaeophorbide-*a* can be catalytically reduced, taking up one molecular proportion of hydrogen. This dihydro-compound yields an oxime and, therefore, still contains its carbonyl group. When dihydrophaeophorbide-*a* was subjected to the "oxo-reaction" no oxoporphyrin, but only phaeoporphyrin-*a* 5 was formed.

[1] Fischer and Riedmair, *Annalen*, 1933, **505**, 87.
[2] Fischer and Medick, *Annalen*, 1935, **517**, 245.

Quantitative examination of the products of oxidation of a number of chlorophyll derivatives showed that they fell into two groups. On the one hand, phaeophorbide-*a* and the chlorins, *e* 4 and *e* 6 yielded small quantities of methylethymaleinimide. On the other hand, dihydrophaeophorbide-*a* and the dihydrochlorins *e* 4 and *e* 6 yielded quantities of the imide approximately double that obtained from the related compounds of the first group. These facts point unmistakably to the presence of a vinyl group in the phaeophorbide and chlorin molecules, and further, the unsaturated group must be in the same position as one of the vinyl groups of protoporphyrin.[1] The " oxo-reaction " can be adequately explained by assuming the addition of hydrogen iodide to the vinyl ethylenic bond, followed by conversion of the iodide into the corresponding secondary alcohol, which is finally oxidized to the ketone. The scheme will make the steps clearer.

$$R{-}CH{=}CH_2 \xrightarrow{HI} R{-}\underset{\displaystyle I}{\underset{|}{CH}}{-}CH_3 \xrightarrow{H_2O} R{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_3 \xrightarrow{O} R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}CH_3$$

The identity of the acetyl group in " oxo-compounds " was put beyond doubt by an examination of oxorhodoporphyrin (VII.). The " oxo-group " of this substance was split off and replaced in turn by bromine, hydrogen and finally an acetyl group. The acetyl derivative proved to be identical with the original oxorhodoporphyrin.[2]

The vinyl group may be attached to either carbon atom 2 or carbon atom 4. A decision was made between these two possibilities by converting phaeophorbide-*a* through pyrophaeophorbide-*a* into oxophylloerythrin (XII.). When this compound was heated in a sealed tube with hydrochloric acid the acetyl group was split off and two new porphyrins were isolated. One of these substances contained one free pyrrole methene group and was a phylloerythrin derivative (XI.). The other was a pyrroporphyrin derivative (XIII.) and contained two free methene groups. Both porphyrins were shown by synthesis to have a hydrogen atom attached to carbon atom 2, and consequently the vinyl group of the original phaeophorbide-*a* must be placed in the same position. The phylloerythrin derivative

[1] Fischer and Breitner, *Annalen*, 1936, **522**, 151.
[2] Fischer and Krauss, *Annalen*, 1936, **521**, 261.

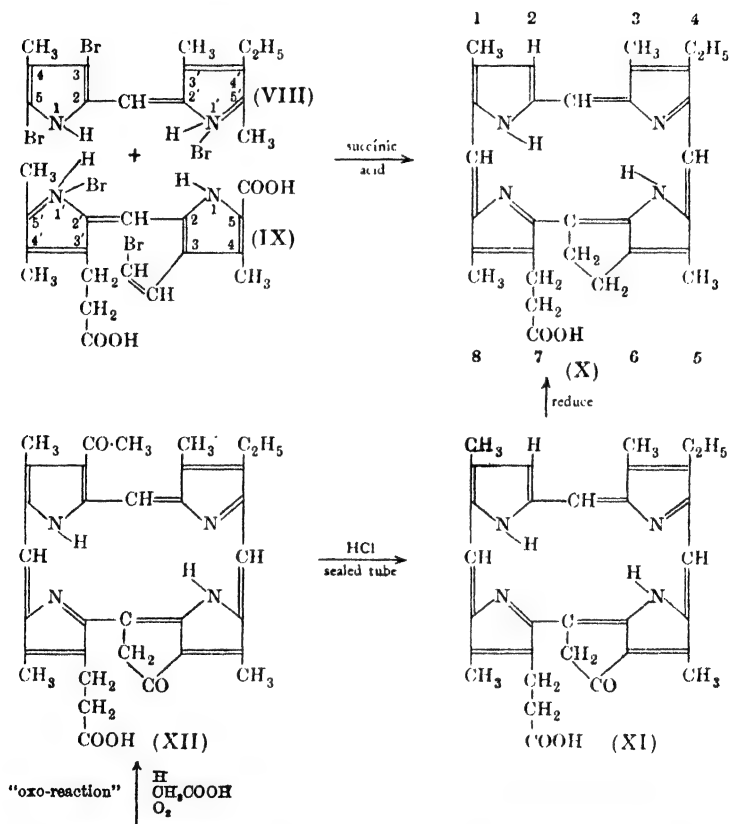
(XI.) from phaeophorbide-*a* was reduced to the corresponding deoxophylloerythrin (X.). This compound was synthesized from 4 : 3′ : 5′-trimethyl-4′-ethyl-3 : 5 : dibromopyrromethene hydrobromide (VIII.) and 5-carboxy-4 : 4′ : 5′-trimethyl-3-bromo vinylpyrromethene-3′-propionic acid hydrobromide (IX.) by fusion with succinic acid.[1] The structures are :

(VIII) + (IX) —succinic acid→ (X)

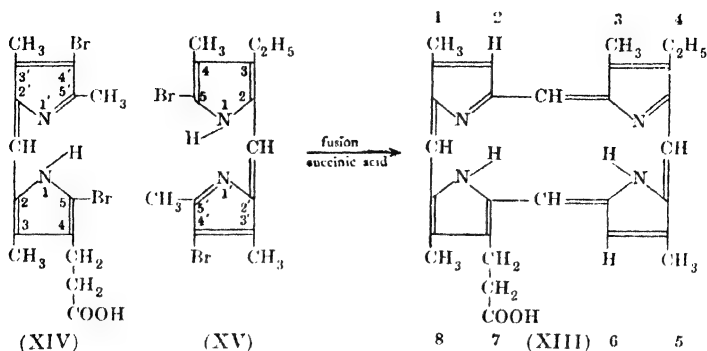
(X) ←reduce— (XI)

(XII) —HCl, sealed tube→ (XI)

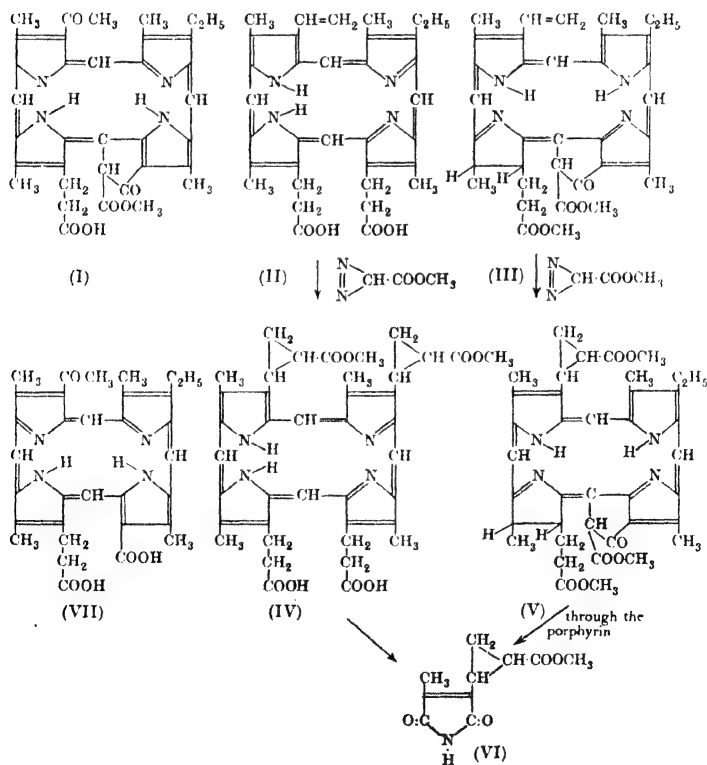
"oxo-reaction" (H, CH₂COOH, O₂): Pyrophaeophorbide-*a* → (XII)

Pyrophaeophorbide-*a* ⟵ Phaeophorbide-*a*

The synthesis of the pyrroporphyrin derivative from 5 : 4′-dibromo - 3 : 3′ : 5′ - trimethyl - pyrromethene - 4 - propionic acid hydrobromide (XIV.) and 5 : 4′ dibromo-4 : 3′ : 5′-trimethyl-3-ethylpyrromethene hydrobromide (XV.) showed it to be 1 : 3 : 5 : 8-tetramethyl-4-ethylporphyrin-7-propionic acid (XIII.).

[1] Fischer and Hasenkamp, *Annalen*, 1934, **513**, 107.
[2] Fischer and Böckh, *Annalen*, 1935, **516**, 177.

(XIV) (XV) (XIII)

On this basis the structures of the other compounds enumerated above will be as follows. The structure of methyl phaeophorbide-*a* (III.) is given provisionally as containing ring IV. partially reduced at carbon atoms 7 and 8.

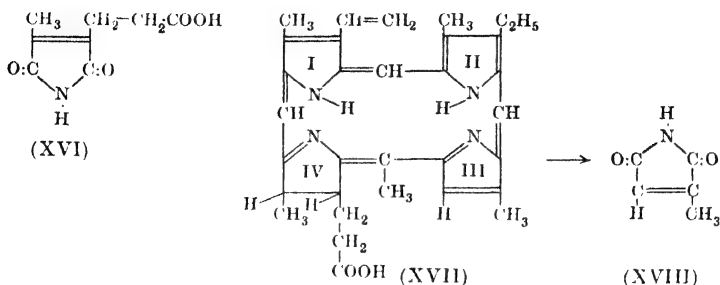
(I) (II) (III)

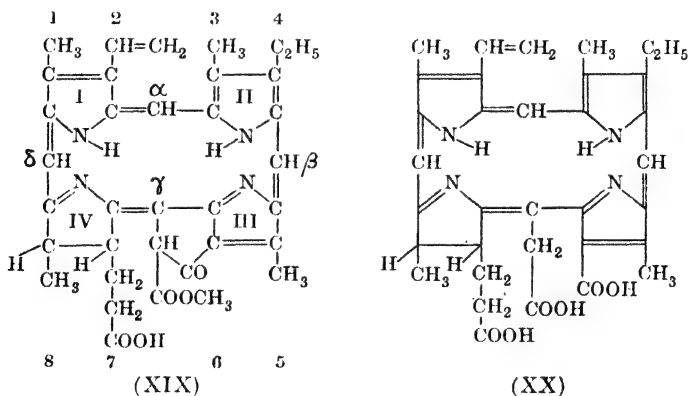
(VII) (IV) (V) (VI)

Phaeophorbide-*a* by the action of hydriodic and acetic acids is converted into the isomeric phaeoporphyrin-*a* 5. This change involves the conversion of a vinyl group into an ethyl group and is accompanied by loss of optical activity. The most obvious conclusion is that one or both points from which the hydrogen atoms are transferred are asymmetric. Inspection of the structure of phaeophorbide-*a* (XIX.) shows that the hydrogen atoms may be placed at a number of positions to produce asymmetry. An indication that the two extra hydrogen atoms in chlorophyll, the phorbides and the chlorins are in a pyrrole nucleus comes from a comparative study of the spectra of these compounds and the porphyrins. The relationship between the visible spectra of these two groups, and the ultra-violet spectra of benzene and *cyclo*hexadiene suggests a partially reduced pyrrole nucleus. The results of comparative potentiometric titrations of chlorophyll derivatives and different substituted pyrroles of known structure have been interpreted as showing the presence of a dihydropyrrole nucleus in the phorbides and chlorins, but not in the porphyrins.[1] The exact positions of the two extra hydrogen atoms have not yet been fixed. Carbon atoms 7 and 8 of ring (IV.) are regarded as the most probable positions for the two extra atoms.

These positions have been selected provisionally on account of the nature of the oxidation products of chlorophyll derivatives, On the one hand porphyrins, which do not contain the "extra" hydrogen atom, yield haematic acid (XVI.). On the other hand, no haematic acid is obtained from chlorins and phorbides. Haematic acid can only come from ring IV. of the chlorophyll derivatives (see formula on p. 160) and the conclusion is that there is some important difference in chemical nature at this ring between the porphyrins and the chlorin-phorbide compounds. It is assumed that the difference in behaviour is due to the reduced condition of the chlorins and phorbides. Rings I. and II. are considered unlikely situations for the "extra" hydrogen atoms as pyrroline compounds, which have been examined, do not yield maleinimides. Chlorophyll derivatives yield methylethylmaleinimide, and those derivatives in which the vinyl group of ring I. has been reduced to an ethyl group give an enhanced yield of the same compound. Inspection of the

[1] Conant and Kamerling, *J. Amer. Chem. Soc.*, 1931, **53**, 3522; Conant, Chow, and Doetz, *ibid.*, 1934, **56**, 2185; Conant and Werner, *ibid.*, 1930, **52**, 449; Conant and Chow, *ibid.*, 1933, **55**, 3745.

structure of phaeophorbide-*a* (XIX.) will make this point clearer. Phyllochlorin (XVII.), which is the chlorin related to phylloporphyrin, yields citraconimide (XVIII.). Here the imide can only come from ring III., which is accordingly rejected as the carrier of the " extra " hydrogen atoms.[1]

(XVI) (XVII) (XVIII)

The structures of phaeophorbide-*a* (XIX.) and chlorin-*e* (XX.) may now be written down. The arrangement of the double bonds is arbitrary, but is thought to agree with the spectroscopic evidence.

(XIX) (XX)

9. *The Structure of Chlorophyll-a*

Taking the structures assigned to phaeophorbide-*a* and phytol as a basis chlorophyll-*a* may now be given the structure (I.).

[1] Fischer and Wenderoth, *Annalen*, 1939, **557**, 170.

(I.) Chlorophyll-*a*

10. *Chlorophyll-b*

Chlorophyll-*b* has the molecular formula $C_{55}H_{70}O_6N_4Mg$. This formula contains one oxygen atom more and two hydrogen atoms less than that of chlorophyll-*a*. The difference is accounted for by the presence of an aldehyde group at carbon atom 3 in place of the methyl group of chlorophyll-*a*.[1] The remainder of the chlorophyll-*b* molecule is given the same structure as in chlorophyll-*a*, as both yield the same porphyrins on degradation and yield other similar derivatives. The extra carbonyl group was detected by the isolation of a dioxime from methyl phaeophorbide-*b*, and its position fixed by the conversion of the trimethyl ester of rhodin-*g* (I.) into 3-demethyldeoxophyllo-erythrin (II.), the structure of which was known.[2]

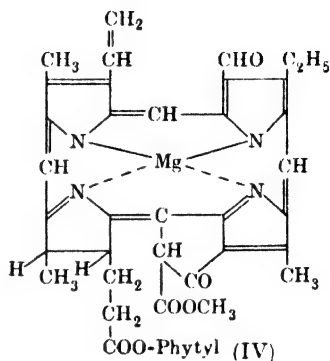
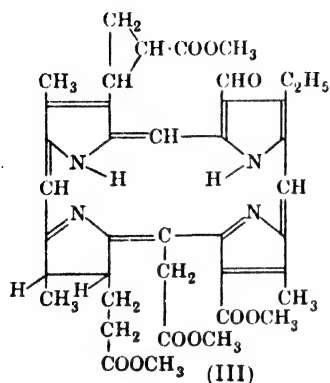
(I) → (II)

[1] Conant, Dietz, and Werner, *J. Amer. Chem. Soc.*, 1931, **53**, 4436; Stoll and Wiedemann, *Helv. Chim. Acta*, 1934, **17**, 456.

[2] Fischer and Bauer, *Annalen*, 1936, **523**, 235; Fischer and Breitner, *Annalen*, 1935, **516**, 61.

The vinyl group was detected by the formation of a *cyclo*-propanecarboxylate (III.) by rhodin-*g* when treated with diazo-acetic ester. As both chlorophylls-*a* and -*b* yield pyrro-, rhodo- and phylloporphyrins the vinyl group is placed at carbon atom 2. On account of these and many other similarities in properties chlorophyll-*b* is given the structure (IV.).

CH₂ CH·COOCH₃ CH₃ CH CHO C₂H₅ CH N H H N CH N N C CH₂ H CH₃ H CH₂ CH₃ COOCH₃ CH₂ COOCH₃ COOCH₃ (III)

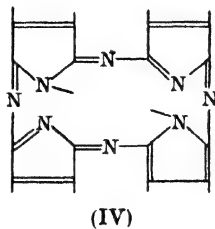
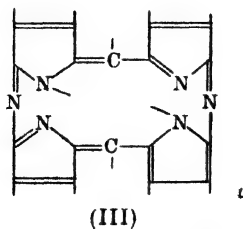
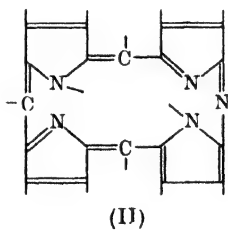
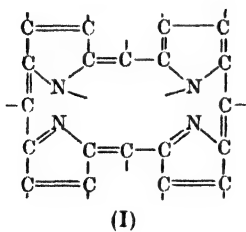
CH₂ CH₃ CH CHO C₂H₅ CH N Mg N CH N N C CH H CH₃ H CH₂ CO CH₃ CH₂ COOCH₃ COO-Phytyl (IV)

CHAPTER VI

THE AZAPORPHYRINS

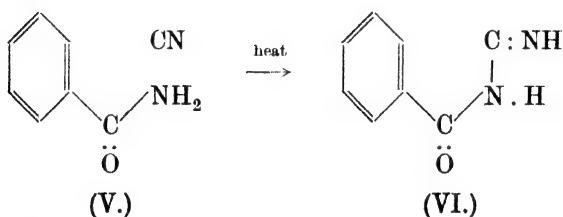
A.—Introductory

These compounds have many features in common with the porphyrins. Like the porphyrins their molecular structure contains four pyrrole nuclei linked together in the form of a sixteen-membered ring. This ring, however, contains one or more nitrogen atoms in place of the methin links of the true porphyrin. They form metallic complexes readily, and are aromatic in character. The complexes are even more stable than the corresponding porphyrins. Thus, they can be dissolved in strong acid and precipitated unchanged by dilution with water. Some of them are very resistant to heat. The structural arrangements of the central rings of a porphyrin (I.), and mono- (II.), di- (III.), and tetra-azaporphyrin (IV.) molecules are shown below for comparison.

(I) (II)

(III) (IV)

None of the azaporphyrins is known to occur naturally. The first compound of this type isolated was prepared from pyridine, cuprous cyanide and *o*-dibromobenzene. This was formulated as a complex pyridine salt, $C_6H_4(CN)_2(C_5H_5N)_2Cu$, and it was not until the iron compound, discovered by accident during the industrial manufacture of phthalimide, was more fully examined that their true molecular nature was made clear. On account of the origin and deep blue colour of the iron complex these compounds were called the phthalocyanines. The phthalocyanines have been shown to contain the tetra-azaporphyrin grouping in the molecule. Their discovery has been followed up energetically and has led to the preparation and the elucidation of the molecular structures of a great variety of azaporphyrins. The phthalocyanines (tetrabenztetra-azaporphyrins) are highly coloured blue to green substances and now occupy a prominent position in industry as pigments and dyes. A remarkable feature of the chemistry of the phthalocyanines is the ease with which the large-ring molecule is formed. Numerous syntheses have been devised having as their basis the production of an intermediate *iso*indole derivative. For example, *o*-cyanobenzamide (V.) yields iminophthalimidine (VI.) by isomerisation, which is readily converted into a phthalocyanine (VII.).

CN, NH_2, C, Ö —heat→ C : NH, N . H, C, Ö

(V.) (VI.)

As the phthalocyanines are the most important members of this group of substances they will be described first.

B.—The Phthalocyanines (tetrabenztetra-azaporphyrins)

1. *The Properties of the Phthalocyanines*

The phthalocyanines form metallic complexes with a wide variety of elements from all groups of the periodic system. They are mostly insoluble in water and the ordinary organic solvents. They can, however, be dissolved in strong acids, and

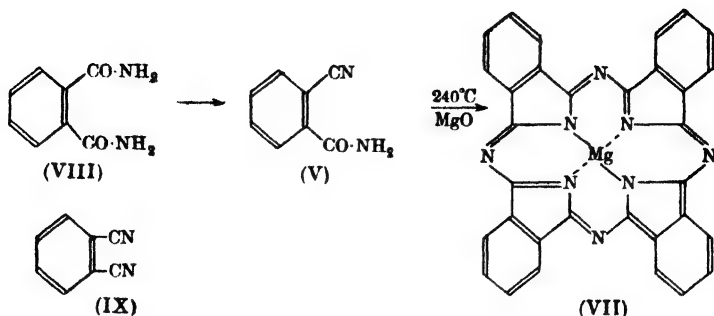
recovered unchanged from these solutions by dilution with water. Some of them are very resistant to heat, and to reducing agents. This unexpected stability is presumably connected with the presence in the molecule of an unbroken system of conjugated double bonds. In contrast with their stability to heat and reducing agents, oxidation leads to the break up of the molecule. Potassium permanganate and other strong oxidizing agents act readily on the compounds giving phthalimide as the main product. The hydrogen atoms of the benzene nuclei of the phthalocyanines cannot be replaced by other atoms or groups as readily as in the case of benzene and its simpler derivatives. Chlorination and sulphonation have, however, been accomplished. The latter process has, as would be expected, the effect of increasing the solubility of the substance.

2. *The Preparation of the Phthalocyanines*

A wide variety of metallic phthalocyanines have been obtained. The metallic derivatives may be prepared from the parent metal-free phthalocyanine, but in practice are obtained from the nitrile-amide or the dinitrile of phthalic acid, the metal being fixed at the same time as the phthalocyanine molecule is formed. The preparation of magnesium phthalocyanine from *o*-cyanobenzamide and magnesium oxide was one of the earliest syntheses successfully accomplished in this series. *o*-Cyanobenzamide (V.) was obtained by the rapid heating of a mixture of phthalamide (VIII.), acetic acid and acetic anydride. Partial dehydration of the diamide took place and *o*-cyanobenzamide was obtained in good yield. The cyanobenzamide was then heated at 240° C. with either magnesium oxide or carbonate in the presence of naphthalene as a diluent. The phthalocyanine (VII.) was freed from impurities by extraction with hot acetone followed by treatment with dilute acid. The phthalocyanine may also be prepared in a similar way using magnesium metal. In this case the compound is isolated as the dihydrate. The metal-free phthalocyanine was obtained when the magnesium compound was treated with cold concentrated sulphuric acid and then diluted in the cold. Crystallization from quinoline yielded the pure substance.[1]

[1] Byrne, Linstead and Lowe, J., 1934, 1017.

$C_6H_4(CO{\cdot}NH_2)_2$ (VIII) ⟶ $C_6H_4(CN)(CO{\cdot}NH_2)$ (V) $\xrightarrow[MgO]{240°C}$ (VII)

$C_6H_4(CN)_2$ (IX)

o-Phthalonitrile (IX.) can be used in place of *o*-cyanobenzamide and reacts very readily with many metals and metallic derivatives. The sodium, calcium, copper, iron and nickel phthalocyanines have been prepared from this starting material. Copper phthalocyanine is obtained in good yield when metallic copper is heated with phthalonitrile at about 210° C. Quantitative control of the reaction shows that the substances react in the proportions of one atom of copper to four molecules of nitrile. When metallic copper is replaced by cuprous chloride and the temperature of the reaction kept at about 170° C., copper phthalocyanine is produced. If, however, cupric chloride is employed, the temperature of the reaction has to be kept above 200° C., and the resulting product is copper monochlorophthalocyanine. Here one chlorine atom enters a benzene nucleus, as it has been shown that fission of the substance by the action of nitric acid yields phthalimide and chlorophthalimide. The readiness with which cuprous chloride combines with phthalonitrile seems to be due to the ease with which it can supply metallic copper. On the other hand, cupric chloride can only act as a source of copper if it simultaneously splits off a chlorine atom.[1]

Copper phthalocyanine is remarkable in that it is an extremely stable substance. Neither molten potash nor boiling hydrochloric acid has any effect on it, and it can be recovered unchanged from solution in concentrated sulphuric acid. It sublimes with some decomposition when strongly heated, but it is quite stable at low pressures in an atmosphere of nitrogen or carbon dioxide when heated to 580° C.

[1] Dent and Linstead, *J.*, 1934, 1027.

Turning to metals other than the divalent members of the periodic classification, univalent sodium yields the disodium phthalocyanine. Tervalent aluminium forms compounds of the type P.Al.X, where P represents the bivalent phthalocyanine group and X a univalent atom or group. Aluminium chloride and free phthalocyanine react to yield chloroaluminium phthalocyanine, P.Al.Cl. From its properties there is no doubt that the chlorine atom is attached to the metallic atom. On the other hand, when aluminium chloride reacts with phthalonitrile, chloroaluminium chlorophthalocyanine is formed. Here the additional chlorine atom is attached to one of the benzene nuclei, and unlike the central chlorine atom, cannot be readily eliminated from the molecule. When the molecule is broken up by oxidation, both phthalimide and a chlorophthalimide are produced. Of the metallic elements of variable valency the tin, platinum and iron compounds have been studied. Tin yields phthalocyanines of the type P : Sn and P : Sn : Cl_2. On the other hand platinous phthalocyanine P : Pt is the only known derivative of this metal. For a description of such compounds as naphthalocyanines, pyridine, thiophen and other porphyrazine derivatives the reader is advised to consult the original papers.[1]

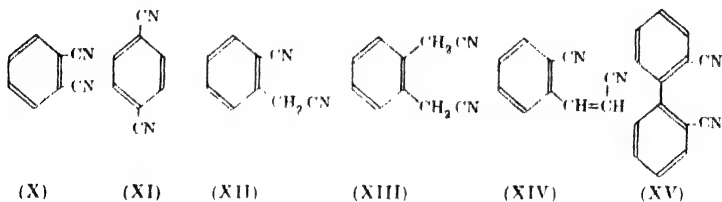
3. *The Structure of the Phthalocyanines*

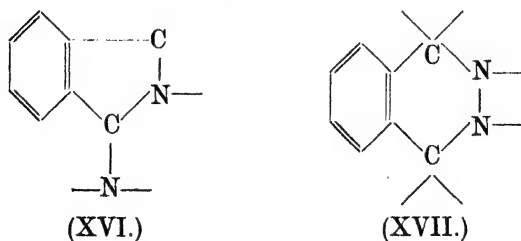
The phthalocyanines are very insoluble substances and consequently it was found very difficult to apply the ordinary methods of molecular weight determination. The magnesium compound, however, was examined by the ebullioscopic method with naphthalene as the solvent. Even in boiling naphthalene the solubility of magnesium phthalocyanine was so small that a very delicate platinum resistance thermometer had to be used in place of the Beckmann thermometer. The mean molecular weight obtained by this method was 551, which agrees very well with the value calculated for $C_{32}H_{16}N_8$ Mg. The percentages of metal in the nickel, copper and platinum phthalocyanines taken into consideration along with determinations of the density and X-ray measurements of the cell dimensions of the

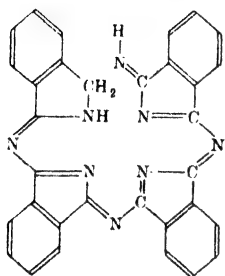
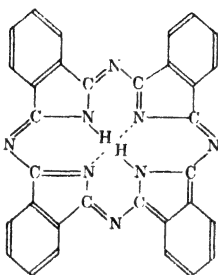
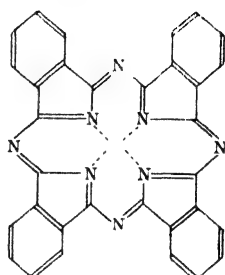
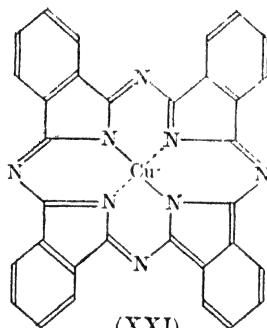
[1] Bradbrook and Linstead, *J.*, 1936, 1745; Linstead et al., *J.*, 1937, 911, 922, 929, 933; Fischer and Endermann, *Annalen*, 1937, 531, 245.

crystals of these compounds gave molecular weight values corresponding to that obtained for the magnesium derivative.[1]

From the methods of preparation and the decompositions of the phthalocyanines it is probable that four $C_8H_4N_2$ units are present in the molecule. Thus hot nitric acid or cold acid permanganate decomposes iron phthalocyanine with the production of phthalimide; hot concentrated sulphuric acid produces phthalic acid, phthalimide, ammonium sulphate and ferrous sulphate, and distillation with soda-lime leads to benzonitrile and ammonia. This view of the structure is supported by the results of quantitative oxidation and by the fact that *o*-phthalonitrile (X.) readily yields phthalocyanines, whilst terephthalonitrile (XI.), homophthalonitrile (XII.), o-xylyl dicyanide (XIII.), *o*-cyanocinnamonitrile (XIV.) and 2 : 2′-diphenonitrile (XV.), give no similar products.

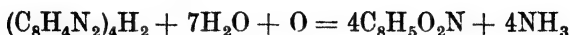
(X) (XI) (XII) (XIII) (XIV) (XV)

The structural unit which best satisfies all the conditions is an *iso*indole ring, with an extracyclic nitrogen atom attached to it (XVI.) to provide the necessary links to form a phthalocyanine molecule. The phthalazine structural unit (XVII.) has been ruled out of consideration as attempts to prepare phthalocyanines from compounds containing this skeleton have failed under a variety of conditions, and in addition it is not obvious how four phthalazine nuclei could be joined to form a large complex ring.

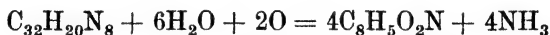
(XVI.) (XVII.)

[1] Robertson, Linstead, and Dent, *Nature*, 1935, 506.

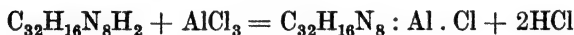
The most reasonable ways in which four *iso*indole units may be joined together through nitrogen atoms to form a larger molecule are shown below. One of these is an open chain structure (XVIII.), and the other two (XIX.) and (XX.), are cyclic in form.

(XVIII) (XIX) (XX)

(XXI)

Structure (XX.) contains no imino-hydrogen atoms and in a metallic derivative such as the copper compound the metallic atom would have to be attached to the nitrogen atoms by co-ordinate links only. Now copper phthalocyanine is an extraordinarily stable substance and it is improbable that the copper atom is held solely in this way by co-ordinate links. Structure (XX.), therefore, cannot be regarded as a suitable representation of phthalocyanines. A choice has been made between the open chain structure (XVIII.) and the cyclic arrangement (XIX.) by means of a quantitative study of the oxidation of phthalocyanine. A suspension of phthalocyanine in dilute sulphuric acid was treated with ceric sulphate at ordinary temperature. Reaction

was rapid and for each four C_8 units exactly one atom of oxygen was absorbed, and about 90 per cent. of the theoretical amount of phthalimide was isolated from the reaction mixture. The oxidation of a molecule of phthalocyanine of structure (XIX.) to phthalimide requires one atom of oxygen and may be represented by the equation,

$$(C_8H_4N_2)_4H_2 + 7H_2O + O = 4C_8H_5O_2N + 4NH_3$$

If, however, phthalocyanine had the open chain structure (XVIII.) each molecule on conversion into phthalimide should take up two atoms of oxygen. The equation here is :

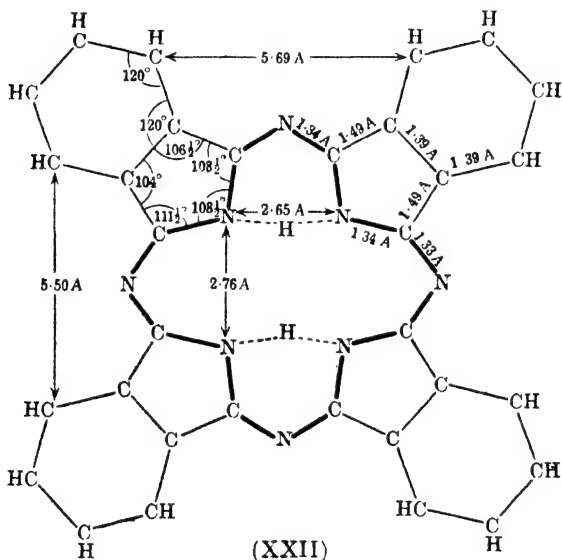
$$C_{32}H_{20}N_8 + 6H_2O + 2O = 4C_8H_5O_2N + 4NH_3$$

Consequently structure (XVIII.) may be rejected and formula (XIX.) taken as best representing phthalocyanine, and the copper derivative will be (XXI.).[1] Independent evidence of the presence of two reactive hydrogen atoms in the phthalocyanine molecule is forthcoming from consideration of the reaction between aluminium chloride and phthalocyanine. The product is chloroaluminium phthalocyanine, $C_{32}H_{16}N_8 . AlCl$, and there is no doubt that the reaction involved is

$$C_{32}H_{16}N_8H_2 + AlCl_3 = C_{32}H_{16}N_8 : Al . Cl + 2HCl$$

These conclusions are supported by the results of X-ray analysis of the compounds.[2] The phthalocyanines were found particularly suitable for exact comparative X-ray examination, and the conclusions arrived at for the metal-free compound and a number of metallic derivatives were that the molecule is square and planar and that the concentration of atoms agrees with the structural arrangement of the molecule arrived at from chemical considerations. The X-ray results also indicate the type of valency bonds in the molecule. The closed ring of sixteen carbon and nitrogen atoms which make up the inner nucleus of the molecule appear to be in a state of double bond-single bond resonance. This inner nucleus is connected to the four benzene rings by bonds $1 \cdot 49 \pm 0 \cdot 03$ Ångstrom units in length pointing to some double bond character at these parts of the molecule. There also appears to be an internal hydrogen bond between

[1] Dent, Linstead and Low, *J.*, 1934, 1033.

[2] Robertson, *J.*, 1935, 615; 1936, 1195; Linstead and Roberston, *J.*, 1936, 1736; Robertson and Woodward, *J.*, 1937, 219; 1940, 36.

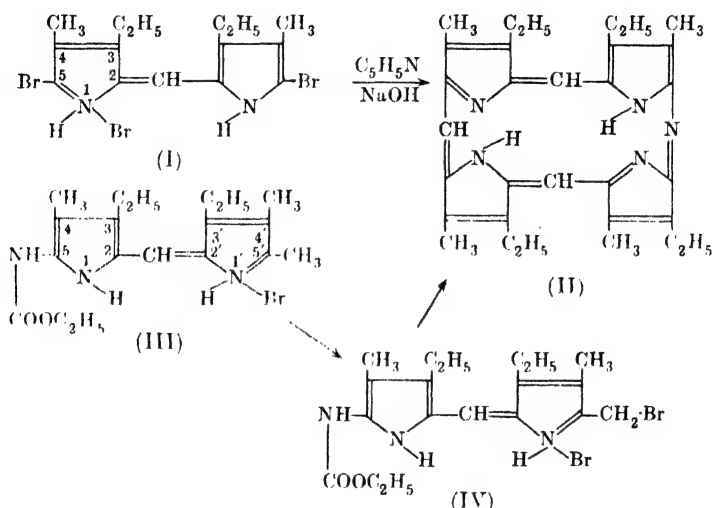
two *iso*indole nitrogen atoms. These ideas are embodied in figure (XXII.) which also shows the molecular dimensions and the structural arrangement of the molecule based on the X-ray analysis of the substance. This is a striking demonstration of the correctness of the structural ideas of organic chemistry. The inner ring system of sixteen carbon and nitrogen atoms is one of great stability, and the interatomic distance has a practically constant value of 1·34Å, whilst the bonds connecting the ring with the benzene nuclei are of quite a different type. Here the interatomic distance is 1·49Å.

(XXII)

C.—The Mono-azaporphyrins

These compounds have the porphyrin structure with one methin group replaced by a nitrogen atom. Mono-aza-aetioporphyrin and several other mono-azaporphyrins have been prepared by a modification of the method found successful for the synthesis of porphyrins from pyrromethenes. Thus when 5 : 5′-dibromo-4 : 4′-dimethyl-3 : 3′diethylpyrromethene hydrobromide (I.) was mixed with pyridine, treated with a solution of sodium hydroxide and then heated mono-aza-aetioporphyrin (II.)

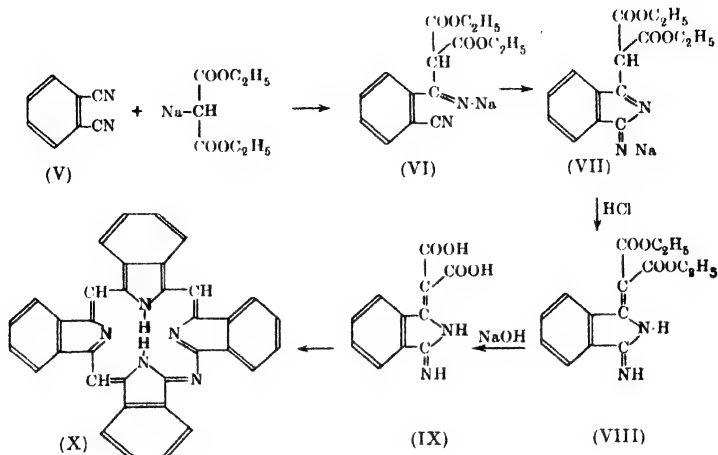
was isolated from the reaction mixture.[1] This azaporphyrin has also been obtained from 5-ethylurethano-4 : 4′ : 5′-trimethyl-3 : 3′-diethylpyrromethene hydrobromide (III.) by the action of bromine in hot acetic acid followed by treatment with boiling sodium hydroxide in quinoline. Here a bromomethyl derivative (IV.) was first formed. Two molecules of this compound then condensed under the influence of the alkaline liquid to yield the aza-aetioporphyrin.[2]

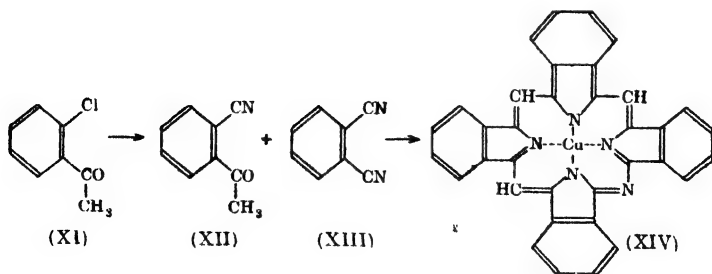
(I) $\xrightarrow[\text{NaOH}]{C_5H_5N}$ (II)

(III) → (IV) → (II)

Turning now to the more complex mono-azaporphyrins containing four benzene nuclei fused in the 3 : 4-position to the pyrrole ring. The most important method and that which gives the best yield has as its starting point phthalonitrile (V.). This compound reacted exothermally in hot alcohol with the sodio-derivative of malonic ester to give an imino-ester (VIII.), from which the imino-acid (IX.) was obtained by boiling for a short time with alkali. It is likely that the first product of this, reaction was the sodio-compound of the "open" ester (VI.), and that this compound by transfer of the sodium atom to the neighbouring cyano-group was converted into the isomeric cyclic compound (VII.), which yielded the imino-ester on treatment with acid.[3]

[1] Fischer and Friedrich, *Annalen*, 1936, **523**, 154 ; Fischer and Müller, *ibid.*, 1937, **528**, 1.

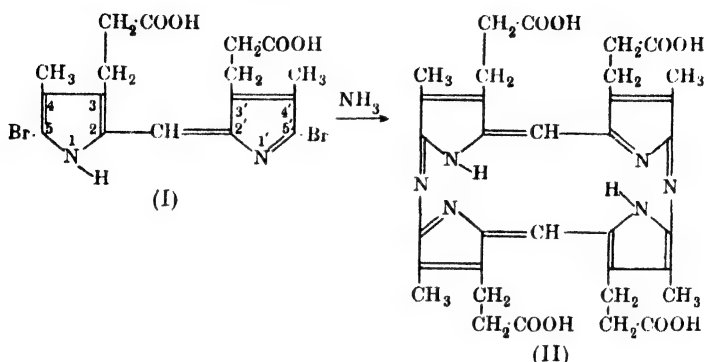
[2] Endermann and Fischer, *Annalen*, 1939, **538**, 172.

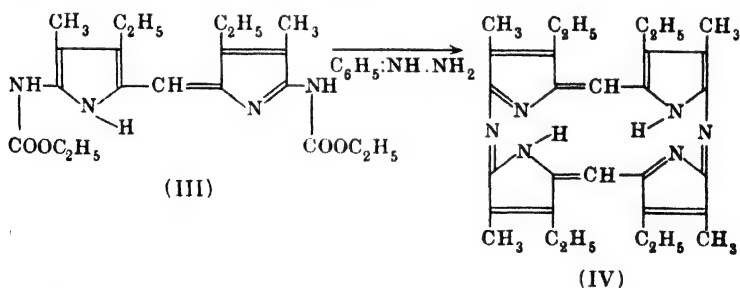
[3] Barrett, Linstead, Leavitt, and Rowe, *J.*, 1940, 1076, 1079.

The imino-acid (IX.) was then heated with zinc dust, and on treatment with hydrochloric acid yielded tetrabenzmono-aza-porphyrin (X.). Like the phthalocyanines tetrabenzmono-aza-porphyrin is a very stable substance and its structure has been confirmed by the method of quantitative oxidation found successful for the phthalocyanines.

The copper derivative of tetrabenzmono-azaporphyrin (XIV.) has been prepared by heating *o*-bromo- or *o*-chloroacetophenone (XI.) with cuprous cyanide in quinoline. The first product of the reaction is *o*-cyanoacetophenone (XII.), and to account for the formation of the azaporphyrin it was assumed that some phthalonitrile (XIII.) was formed during the change and entered into the reaction.[1]

[1] Helberger, *Annalen*, 1937, **529**, 205; Helberger and Rebay, *ibid.*, 1937, **531**, 279.

D.—The Di- and Tri-azaporphyrins

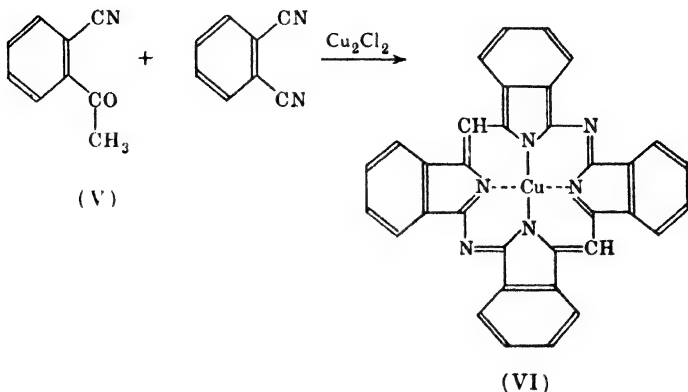
Some of these compounds have been obtained by the methods described for the preparation of monoazaporphyrins, and the first diazaporphyrin (II.) was prepared by the action of ammonia on 5 : 5′-dibromo-4 : 4′-dimethyl-3 : 3′-di-β-carboxyethylpyrromethene hydrobromide (I.).[1]

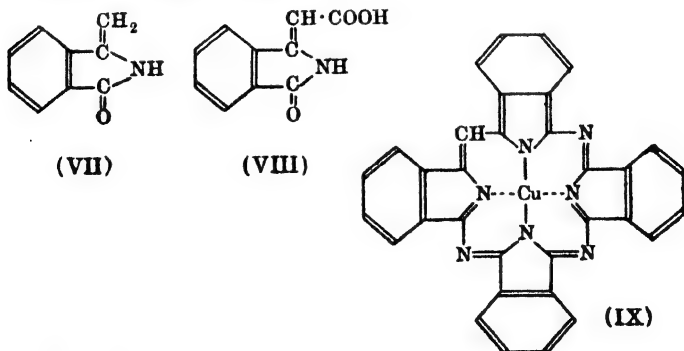
(I) $\xrightarrow{NH_3}$ (II)

Similarly it was found that substituted aminopyrromethenes on suitable treatment yielded diazaporphyrins. Thus two molecules of 5 : 5′-diethylurethano-4 : 4′-dimethyl-3 : 3′-diethylpyrromethene (III.) condensed readily to give the β δ-diazaaetioporphyrin (IV.). This condensation takes place in a variety of conditions, but most readily under the influence of phenylhydrazine.[2]

(III) $\xrightarrow{C_6H_5 \cdot NH \cdot NH_2}$ (IV)

The copper derivative of tetrabenzdiazaporphyrin (VI.) results when *o*-cyanoacetophenone (V.), *o*-phthalonitrile and cuprous chloride in the proportions of 2 : 1 : 2 are heated in quinoline.[3]

[1] Fischer, Haberland, and Müller, *Annalen*, 1936, **521**, 122.
[2] Metzger and Fischer, *Annalen*, 1937, **527**, 1.
[3] Helberger and Rebay, *Annalen*, 1937, **531**, 279.

(V)

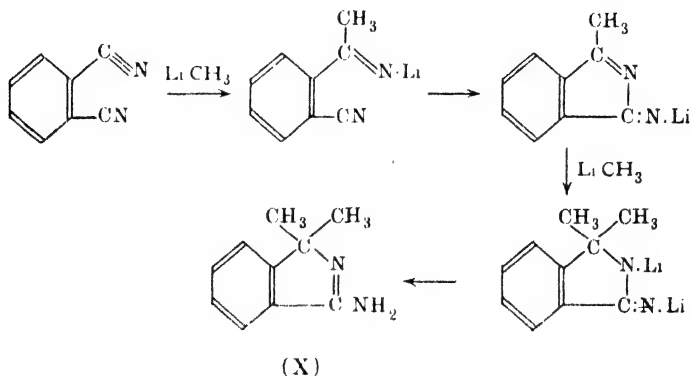
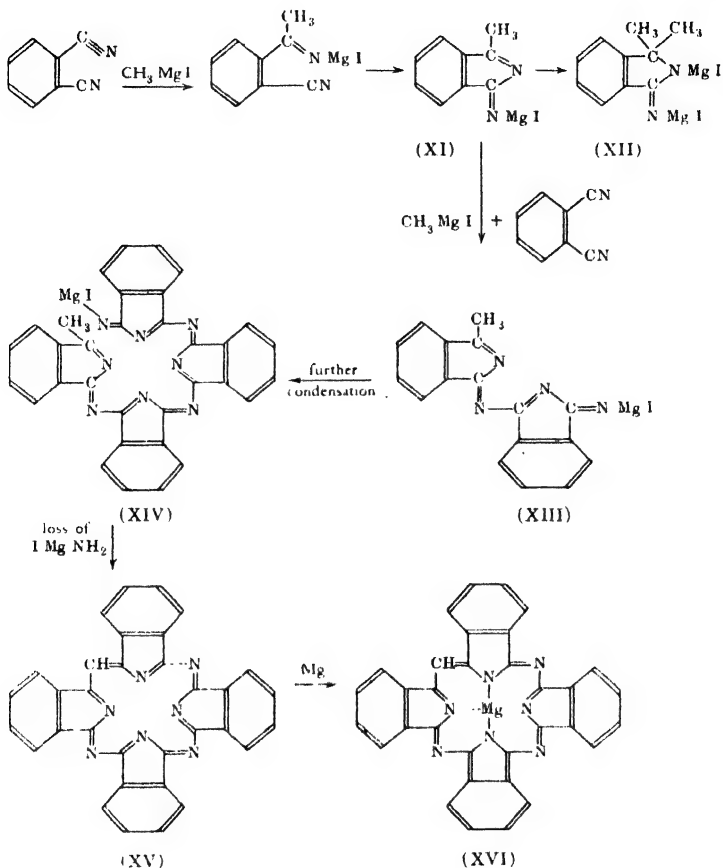
(VI)

No simple triazaporphyrin has yet been isolated in a pure condition. The copper derivative of tetrabenztriazaporphyrin (IX.) has, however, been prepared from *o*-cyanoacetophenone, *o*-phthalonitrile and cuprous cyanide by the method employed to produce tetrabenzdiazaporphyrin (VI.). It was found that by increasing the proportion of phthalonitrile in the reaction mixture the main product was the triaza-compound.[1] The triazaporphyrin is also formed when methylene phthalimidine (VII.) or phthalimidene acetic acid (VIII.), phthalonitrile and copper are heated together.[2] This phthalimidine reaction is an important one, as not only may the two derivatives mentioned above be employed in these syntheses, but a number of other derivatives have also been used successfully.[3]

(VII) (VIII) (IX)

[1] Helberger and Rebay, *Annalen*, 1937, 531, 279.
[2] Dent, *J.*, 1938, 1.
[3] Helberger, Rebay, and Hever, *Annalen*, 1938, 533, 197; 536, 173.

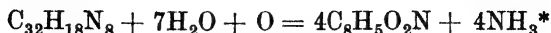
From the constitutional point of view the most interesting syntheses of tetrabenztriazaporphyrin is from phthalonitrile and either methylmagnesium iodide or methyl-lithium. This synthesis gives an insight into the mechanism of the formation of the triaza-compound, and affords a ready explanation of the intermediate steps in the preparation.

When an excess of methylmagnesium iodide or methyl-lithium acts on *o*-phthalonitrile, 3-amino-1 : 1′-dimethyl*iso*indole (X.) is formed. The following steps explain this reaction,

$C_6H_4(C{\equiv}N)(CN) \xrightarrow{LiCH_3} C_6H_4(C(CH_3){=}N{\cdot}Li)(CN) \longrightarrow$ ring with $C(CH_3){=}N$ and $C{:}N.Li$ $\xrightarrow{LiCH_3}$ ring with $C(CH_3)_2$, $N.Li$ and $C{:}N.Li$ $\longrightarrow$ ring with $C(CH_3)_2$, $N{=}C{\cdot}NH_2$

(X)

This gave the clue to the mechanism of the formation of tetrabenztriazaporphyrin, which is also formed from methylmagnesium iodide or methyl-lithium and *o*-phthalonitrile under modified conditions. It is concluded that the single methin link of the triazaporphyrin is provided by an intermediate compound such as (XI.) or (XII.), and that unchanged *o*-phthalonitrile is responsible for the three nitrogen links. *o*-Phthalonitrile yields some of the compound (XI.) or (XII.), which then reacts with unchanged nitrile and methylmagnesium iodide (or methyl-lithium) to produce the di*iso*indole derivative (XIII.). This substance on further reaction with nitrile and Grignard reagent yields the tetra*iso*indole compound (XIV.), which by loss of I . Mg . NH_2 and ring closure gives rise to the unstable dehydro-compound (XV.). Finally this compound by rearrangement of its valencies acquires a magnesium atom to form magnesium tetrabenztriazaporphyrin (XVI.). The scheme of structures given below makes the steps clear.

In dealing with the mono- and di-azaporphyrins the structural parallel with the phthalocyanines was assumed as a working basis. In the case of the tetrabenztriazaporphyrins all the evidence forthcoming leaves no doubt that the assumption is correct. An X-ray examination of tetrabenztriazaporphyrin and a comparison of the results with those obtained from phthalocyanine showed that the two structures, dimensions and arrangements of the molecules in the crystals are practically identical. The results of quantitative oxidation point in the same direction. Phthalocyanine and its metallic derivatives when oxidized by acid ceric sulphate absorb one atomic proportion of oxygen to

give a quantitative yield of phthalimide in accordance with the equation

$$C_{32}H_{18}N_8 + 7H_2O + O = 4C_8H_5O_2N + 4NH_3{}^*$$

Now tetrabenztriazaporphyrin contains one methin bridge and in complete oxidative fission of the molecule this group should yield carbon dioxide in addition to phthalimide and ammonia. The equation representing the process should, therefore, be,

$$C_{33}H_{19}N_7 + 5H_2O + 5O = 4C_8H_5O_2N + 3NH_3 + CO_2$$

This change has been realized quantitatively. The action of ceric sulphate showed that the amount of oxygen absorbed corresponded to five atoms for each molecule of the triaza-porphyrin broken up, and that one molecule of carbon dioxide was formed. Permanganate oxidation of tetrabenztriaza-porphyrin gave a yield of 84 per cent. of phthalimide with the liberation of three molecular proportions of ammonia. The equation is thus fully confirmed, and all the experimental evidence gives sound support to the structural ideas put forward.[1]

* See page 170.

[1] Barrett, Linstead, Tuey, and Robertson, *J.*, 1939, 1809; Barrett, Linstead, Rundall, and Tuey, *J.*, 1940, 1079.

CHAPTER VII

SYNTHETIC HIGH POLYMERS AND CONDENSATES

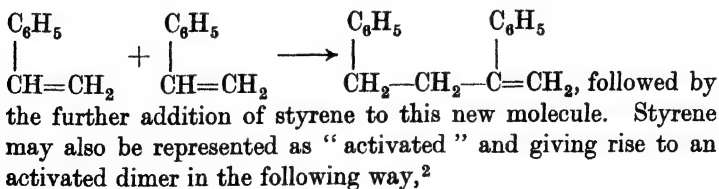
A. Introductory

These substances may be viscous liquids, hard and glass-like or amorphous rubber-like solids. The rapid industrial development of some of these synthetic materials is due to the similarity of their properties to those of natural resins and rubber, and what adds to their importance is the fact that the degree of polymerization or condensation can be controlled to yield products with a variety of properties. Thus from phenol and formaldehyde both liquid and solid resins may be obtained, and styrene yields a series of polymers of widely different physical properties.[1] The study of these large molecules has proceeded along two main lines. On the one hand the methods of organic chemistry have yielded outstanding results, particularly in the synthetic field. On the other hand, the resources of physics and physical chemistry have been utilized with notable effect in the study of the mechanisms of molecular formation.

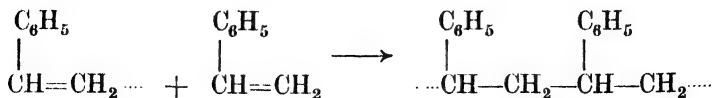
Large molecules containing a great number of small repeating units can be synthesized either by polymerization or by the elimination of simple molecules such as water, alcohol or ammonia from suitable compounds.

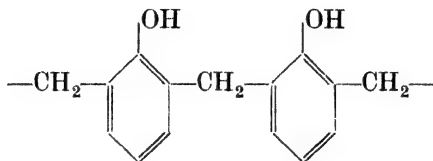
Taking styrene as an example of an unsaturated substance, polymerization could proceed thus :

$$\begin{array}{l} C_6H_5 \\ | \\ CH{=}CH_2 \end{array} + \begin{array}{l} C_6H_5 \\ | \\ CH{=}CH_2 \end{array} \longrightarrow \begin{array}{l} C_6H_5 \\ | \\ CH_2{-}CH_2{-}\!\!\!\end{array}\begin{array}{l} C_6H_5 \\ | \\ C{=}CH_2, \end{array}$$

followed by the further addition of styrene to this new molecule. Styrene may also be represented as " activated " and giving rise to an activated dimer in the following way,[2]

[1] Baekeland, *Ind. Eng. Chem.*, 1912, **4**, 739 ; Staudinger et al., *Ber.*, 1929, **62 B**, 241.

[2] Dostal, Mark, and Raff, *Ind. Eng. Chem.*, 1937, **29**, 595 ; Risi and Gauvin, *Canadian J. Res.*, 1936, **14** (Sec. B), 225 ; Staudinger, *Die hochmolekularen organischen Verbindungen*, Berlin, 1932.

$$\underset{\overset{|}{C_6H_5}}{CH{=}CH_2}\cdots + \underset{\overset{|}{C_6H_5}}{CH{=}CH_2} \longrightarrow \cdots\underset{\overset{|}{C_6H_5}}{CH}{-}CH_2{-}\underset{\overset{|}{C_6H_5}}{CH}{-}CH_2\cdots$$

A great variety of unsaturated compounds can be polymerized to substances of high molecular weight and these may contain identical or mixed small units. Large synthetic condensates are also many and varied, ranging from such combinations as polyamides $—NH—(CH_2)_n—CO—NH—(CH_2)_n—CO—$ to products from phenol and formaldehyde

$$—CH_2—C_6H_3(OH)—CH_2—C_6H_3(OH)—CH_2—$$

Products such as these may have their terminal valencies saturated by monovalent groups, or possibly the large molecule may be in the form of a ring.

The phenol-formaldehyde product (Bakelite) is of interest as it was developed in the early days of the present century, and was the first synthetic resin to be successfully exploited for commercial purposes.

Large molecules are not limited to the linear type illustrated above, as more complex structures may arise by cross-linking in two or three dimensions. The essential condition necessary for the formation of macromolecules is the presence in the simple molecules of (*a*) unsaturation, (*b*) a ring structure or (*c*) two or more reactive centres through which one molecule may interact with another. It is obvious that an aminohydroxy acid and phenol-formaldehyde belong to the last-named type, and styrene to the first group.

The phenol-formaldehyde condensation product represented above is capable of reacting at the further points, hydroxyl and *para*-hydrogen of the benzene nucleus, and in this way giving rise to more complex three-dimensional macromolecules. The physical properties of the product isolated depend on the degree of condensation and the substance at the first stage of combination may be soluble and fusible, while at a second stage the product is less soluble and fused with difficulty. When the

final stage of condensation is reached, the product is insoluble and infusible. On the other hand, the long chain or thread macromolecules are normally soluble at all stages of polymerization or condensation.

The macromolecular end-products usually obtained by polymerization and condensation are not pure compounds as we think of the word pure applied to simple substances. They are mixtures of molecules having the same empirical formula but varying in size, and even in structure. Attempts, partially successful, have, however, been made to obtain uniform products by methods based on ultracentrifugal separation and fractional solution and precipitation.

B. The Relationship between Structure and Polymerization Capacity

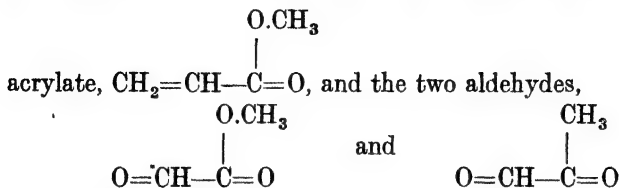
From both the theoretical and practical points of view the rate of polymerization of unsaturated compounds is important, and many comparisons of the speeds of addition have been made. Some qualitative conclusions can be drawn from the experimental facts. An increase in unsaturation in the simple molecule leads to an increase in the rate of polymerization. Thus at 750° C. ethylethylene, $CH_3—CH_2—CH=CH_2$, polymerizes at a measureable speed, whereas 1 : 3-butadiene, $CH_2=CH—CH=CH_2$, is converted into a high polymer at a much lower temperature, and vinylacetylene, $CH_2=CH—C \equiv CH$, combines with itself with explosive rapidity on being heated. It will be noted, however, that both 1 : 3-butadiene and vinylacetylene contain conjugated systems of unsaturation and that this new factor must be taken into consideration. In fact, it is well known that compounds containing conjugated systems of ethylenic bonds polymerize more rapidly than substances in which the unsaturated links are unconjugated. Thus a comparison of the rates of reaction of 1 : 3-pentadiene and 2 : 3-pentadiene, shows that the 1 : 3-compound polymerizes at approximately double the rate of the 2 : 3-diene.[1]

[1] Coffin and Maas, *J. Amer. Chem. Soc.*, 1928, **50**, 1427; Wheeler and Wood, *J.C.S.*, 1930, 1819; Lebedev and Shawronskaja, *J. Russ. Phys. Chem. Soc.*, 1912, **43**, 1124; *Chem. Zentr.*, 1912, **1**, 1440; Vaughan, *J. Amer. Chem. Soc.*, 1932, **54**, 3863; Jacobson and Carothers, *J. Amer. Chem. Soc.*, 1933, **55**, 1622; Kyriakides, *J. Amer. Chem. Soc.*, 1933, **55**, 3431.

This influence of conjugation holds, not only for systems of ethylenic and acetylenic bonds, but also for systems in which all or part of the conjugation is made up of carbonyl groups. Not only does 1 : 3-butadiene polymerize with ease, but the two vinyl derivatives acrolein, $CH_2{=}CH{-}CH{=}O$, and methyl

$$\begin{array}{c} O.CH_3 \\ | \\ CH_2{=}CH{-}C{=}O \end{array}$$

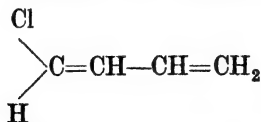
acrylate, $CH_2{=}CH{-}C(O.CH_3){=}O$, and the two aldehydes,

$$\begin{array}{c} O.CH_3 \\ | \\ O{=}CH{-}C{=}O \end{array} \quad \text{and} \quad \begin{array}{c} CH_3 \\ | \\ O{=}CH{-}C{=}O \end{array}$$

also combine readily to form polymers.[1]

Here again interpretations of results must be made with reserve as vinyl derivatives containing negative groups, whether conjugated or unconjugated polymerize readily. For example

$$\begin{array}{c} CH_3 \\ | \\ CH_2{=}CH{-}O{-}C{=}O \end{array}$$

vinyl acetate, $CH_2{=}CH{-}O{-}C(CH_3){=}O$, and vinyl chloride, $CH_2{=}CH{-}Cl$, containing no conjugation polymerize with ease. The dominating factor here is undoubtedly the negative group as ethylene and propylene (methylethylene) do not polymerize with the readiness of styrene, methyl acrylate, methyl vinyl ketone and other negatively substituted ethylenes. This effect of negative substituents is also evident in the dienes. A comparison of the rates of polymerization of 1 : 3-butadiene and its derivatives brings out some interesting points. Here the position of the substituent in the molecule has a marked effect. When a chlorine atom replaces one of the hydrogen atoms of carbon atom 1 of 1 : 3-butadiene the product,

$$\begin{array}{l} Cl \\ \quad \rangle C{=}CH{-}CH{=}CH_2 \\ H \end{array}$$

polymerizes somewhat faster than butadiene, but when the

$$\begin{array}{c} Cl \\ | \\ CH_2{=}C{-}CH{=}CH_2 \end{array}$$

chlorine atom is in the 2-position, $CH_2{=}C(Cl){-}CH{=}CH_2$ (chloroprene) the activating influence is so great that the rate of reaction

[1] Staudinger, *Trans. Faraday Soc.*, **1936, 32, 97.**

is increased several hundred times. Bromine and iodine substituted in the 2-position of butadiene have an even more marked effect on the rate of polymerization.[1] The introduction of a second chlorine atom into butadiene, at the 3-position,

$$CH_2{=}\underset{\mathrm{Cl}}{C}{-}\underset{\mathrm{Cl}}{C}{=}CH_2$$

$CH_2{=}C(Cl){-}C(Cl){=}CH_2$, still further enhances the rate of polymerization, which has been estimated to be approximately three times the speed of the reaction of the 2-chloro-derivative. A phenyl group in the 2-position of butadiene also has a strong effect on the speed of reaction, but not so marked as in the case of the 2-chloro-compound.[2] The replacement of a hydrogen atom attached to carbon atom 2 of butadiene by a methyl group leads to isoprene, which polymerizes somewhat faster than butadiene. If, however, the methyl group is at carbon atom 1, the rate of polymerization drops to approximately a third of that of butadiene.[3] This depressing effect of an alkyl group at the terminal position of butadiene is a general one and has been recorded for ethyl, butyl and heptyl groups in addition to the methyl radicle. Certain cyclic compounds polymerize readily. For example 1 : 3-*cyclo*-hexadiene yields a high polymer, and *cyclo*pentadiene, even more readily, passes into its polymers. The presence of a benzene ring fused to the five-membered ring does not appreciably affect the polymerization, as indene gives rise to polyindenes, which have been stated to contain as many as fifty indene units in the molecule.

A great many compounds containing the carbonyl group are capable of polymerization. The facts concerning the polymerization of formaldehyde and acetaldehyde are well known, and the polyoxymethylenes prepared from formaldehyde are of great theoretical interest. In addition, acrolein, $CH_2{=}CH{-}CH{=}O$, methyl glyoxalate, $O{=}C(OCH_3){-}CH{=}O$, pyruvic aldehyde, $CH_3{-}CO{-}CHO$, glyoxal, $O{=}CH{-}CH{=}O$ and the ketens, $R_2 : C = C = O$ may be mentioned as other illustrations of

[1] Carothers et al., *J. Amer. Chem. Soc.*, 1931, **53**, 4203 ; 1933, **55**, 789, 2004.
[2] *Idem, ibid.*, 1933, **55**, 2807 ; *Ind. Eng. Chem.*, 1934, **26**, 30 ; *Chemical Reviews*, 1931, **8**, 353.
[3] Whitby et al., *Canadian J. Res.*, 1932, **6**, 203, 280.

carbonyl compounds which polymerize readily.[1] Constitutional effects may be traced here too. The aldoketen, $\begin{matrix} CH_3 \\ H \end{matrix}\!\!>C=C=O$ polymerizes more readily than the ketoketen, $\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>C=C=O$ and the double keten, carbon suboxide, $O=C=C=C=O$, reacts with itself relatively slowly.[2]

The unsaturated compounds polymerize under such a variety of conditions that exact comparisons are difficult and it must be borne in mind that in some cases errors may have crept in due to the presence of oxygen or traces of other catalysts. Even small variations like changes of pressure in the reaction tube could lead to conclusions which would make comparisons of polymerization rates of doubtful value.

C. The Reaction Factors

High polymers may be formed from the gaseous condition, in the pure liquid state, in solution or in emulsions. The monomers may be activated by heat, pressure, catalysts, light (particularly ultra-violet rays), mercury vapour sensitized by light, the silent electric discharge and α-particles. In some cases the use of a combination of these factors is found desirable. On the other hand, many substances are known which modify, retard or inhibit polymerizations, and have their uses in controlling the degree of polymerization and the length of the molecular chain of linear polymers. Modifying agents include such compounds as mercaptans, amines and quinols.

The polymerization of gaseous hydrocarbons has received attention both on account of theoretical considerations, and because of the production of large amounts of natural hydrocarbon gases and gases from petroleum oil cracking processes. The polymerization of the unsaturated gases from the sources mentioned is very slow at low temperatures in the absence of catalysts, but is readily effected by the catalytic action of

[1] Harries and Temme, *Ber.*, 1906, **40**, 165; Meisenheimer, *ibid.*, 1912, **45**, 2635.

[2] Staudinger, 1912, *Die Ketene*.

sulphuric acid, phosphoric acid and phosphates, aluminium chloride and many other materials.[1] For example *iso*butene reacts with sulphuric acid at ordinary temperature and is converted into tertiary butyl alcohol, and when the reaction mixture is heated decomposition of the alcohol leads to the formation of di-*iso*butene $(CH_3)_3C—CH_2—C(CH_3)=CH_2$, which can be reduced to *iso*-octane, the standard motor fuel hydrocarbon for high anti-knock efficiency.[2] The polymerization of gaseous formaldehyde to polyoxymethylenes takes place readily under the influence of ultra-violet light of 3000 Å. in the presence of traces of formic acid as a promoter, and when the formic acid was present to the extent of a few per cent. the polymerization took place rapidly in the dark at pressures below atmospheric.[3] In gaseous polymerizations the transition from monomer to polymer is accompanied by a decrease in volume, and consequently such reactions are favoured by pressure. Heat, as would be expected, in general accelerates the rate of polymerization, but secondary decomposition effects have to be taken into account, and in some cases high temperature reactions lead to comparatively simple polymers as end products.[4] Moderate temperatures have, however, beneficial effects on polymerizations. In the case of chloroprene, which can give rise to a number of closely related high polymers, the transformation into the μ-polymer takes place about four times as fast at 62° C. as at 25° C. The most suitable temperature for the formation of the simpler α-polymer is 35° C. Some polymerizations, particularly in the olefine group, proceed more readily at low temperatures in the presence of catalysts. For example, pentenes, with aluminium chloride as the catalyst, polymerize rapidly at − 80° C., and *iso*propylethylene, under the same experimental conditions, yields a polymerized liquid of high viscosity. Polymerizations at a constant temperature and in the absence of catalysts in the liquid phase are influenced by pressure and it has been found in general that uncatalyzed

[1] Ipatieff, Corson, and Egloff, *Ind. Eng. Chem.*, 1935, **27**, 1069, 1077.

[2] Dunstan, Hague, and Wheeler, *J.S.C.I.*, 1931, **50**, 313; 1932, **51**, 131; *Ind. Eng. Chem.*, 1934, **26**, 307; Frolich and Wiezevich, *ibid.*, 1932, **24**, 13; Dunstan, *Trans. Faraday Soc.*, 1936, **32**, 227.

[3] Carruthers and Norrish, *Trans. Faraday Soc.*, 1936, **32**, 195.

[4] Whitby and Crozier, *Canadian J. Res.*, 1932, **6**, 203.

reactions which proceed slowly at ordinary pressures are considerably accelerated at high pressures. Substances which do not combine at ordinary pressures cannot be made to unite at even great pressures.[1] Thus acrolein kept for 16 hours at 110° C. and 1 atmosphere pressure polymerized to the extent of 3·8 per cent., but when the pressure was raised to 3000 atmospheres the percentage conversion was 87. When α-methylstyrene was heated alone at ordinary pressures the trimer was the highest polymer produced, but at 5000 atmospheres pressure and 100° C. 85 per cent. of the compound was converted into a mixture of polymers with a mean molecular weight of 5600, corresponding to an aggregation of about 50 α-methylstyrene molecules.[2] The effect of pressure on the rate of polymerization of isoprene has been extensively studied and under comparable conditions it has been found that the rate increases approximately 6000 times at ordinary temperature between pressures of 2000 and 18,000 atmospheres.[3] On the other hand, acetaldehyde at 40° C. was unchanged by pressures up to 9000 atmospheres, and ethylene oxide was recovered unchanged after being heated to 150° C. at 3000 atmospheres pressure.

In some cases it is necessary to reduce the rate of reaction, and here dilution with an inert solvent is the most satisfactory method of controlling polymerization. The solubility of a compound of the chain type in a solvent frequently depends on the molecular chain length, and it is possible to carry out polymerization in certain solvents or mixtures of solvents so that long chain molecules as they are formed are precipitated from the solution, the shorter chain molecules remaining in solution. In this way more homogeneous products are obtained. Dilution of the monomer may also be affected by means of emulsification. Polymerization under these conditions has certain technical advantages such as reduction of the reaction time, lowering of the temperature, and ease of handling the polymerized product in the emulsified condition.[4] Emulsification finds its principal applications in the manufacture of synthetic rubbers, and mixed

[1] Fawcett and Gibson, *J.*, 1934, 386.

[2] Sapiro, Linstead, and Newitt, *J.*, 1937, 1784.

[3] Conant et al., *J. Amer. Chem. Soc.*, 1930, **52**, 1659; 1932, **54**, 628; Tammann and Pape, *Z. anorg. Chem.*, 1931, **200**, 113.

[4] Williams and Walker, *Ind. Eng. Chem.*, 1933, **25**, 199; Whitby and Katz, *ibid.*, 1933, **25**, 1204, 1338.

polymers like butadiene-styrene and vinyl chloride-methyl acrylate are conveniently prepared in good yields in this way. The time of polymerization is reduced and the resulting emulsion (latex) contains the polymer in a form more readily handled than solid material obtained by other methods of polymerization. The usual methods of emulsification are employed: emulsifying agents such as sodium oleate or naphthalene sulphonates, along with protective colloids to increase the stability of the mixture, have been found satisfactory. To these the monomer or mixture of monomers is added with a suitable catalyst, usually of the oxidizing type such as hydrogen peroxide or a salt of one of the per-acids. The most suitable emulsifying agent and catalyst for any given polymerization are found by experience. Other conditions such as the hydrogen ion concentration of the liquid, and the quantity of modifying agent necessary to give the best yield, have to be carefully adjusted.

The presence of traces of some compounds retards polymerization in many cases. Thus 0·1 per cent. of quinol reduces considerably the yield of polymerized acrolein, sulphur retards the polymerization of vinyl acetate and the combination of divinyl ether with itself is almost completely inhibited in the presence of traces of ammonia.

Catalysis plays an important part in polymerizations, and the substances which have been used as catalysts may be grouped in five broad classes according to their chemical nature. These classes are the metals, oxidizing agents including oxygen, halides, inorganic and organic acids and bases. In addition to these five large groups, carbon, clays and certain stable oxides such as silica are of considerable importance. A great variety of metals from lithium to platinum have been used, with sodium occupying the most important position. The oxidizing agents include ozone, peroxides and per-salts. Of the halides aluminium chloride has found the largest number of applications. Among the acids sulphuric and phosphoric acids have been extensively applied in the polymerization of the simpler olefins. On the other hand bases have found their chief use in the phenol-formaldehyde type of condensation.*

* NOTE.—For further information on polymerization catalysts the reader should consult the excellent text *Polymerization*, by Burk, Thompson, Werth and Williams, American Chemical Society Monograph, 1937.

From this brief description of the more important factors which influence polymerization, it is evident that the experimental conditions, even for the polymerization of any one substance, may be varied within wide limits. Butadiene, for example, can be polymerized in many different ways; over a wide range of temperature, at high and low pressures, catalyzed and uncatalyzed, in emulsion and in the gaseous condition or in solution. The effects on this compound of photo-polymerization at various temperatures and pressures, alternating current and α-particles have also been investigated.

D.—Some High Polymers and Condensates

1. *Polystyrenes*

(*a*) *General.*—Polystyrene is one of the best known thermoplastic materials. The conversion of liquid styrene into a gelatinous solid by heat was recorded more than one hundred years ago, and since then the products obtained from styrene have, from time to time, been examined. During the past fifteen years many facts concerning the polymerization processs have been accumulated. Styrene may be polymerized in a great variety of ways.[1] On heating or merely on standing at room temperature its viscosity increases until an elastic jelly is formed, and this material may pass into a hard brittle mass. The process of polymerization of styrene is greatly accelerated by light and a variety of catalysts. The molecules of the polystyrenes are considered to be long chains built up in regular fashion from styrene units. In the conversion of styrene into the polymer the unsaturation of styrene disappears except one double bond in each molecule of polymer. This degree of unsaturation appears to be independent of the size of the molecule.[2] The number of simple styrene units contained in a single macromolecule depends on the conditions of polymerization. When the polymerization is rapid, as in the case when stannic chloride is used at ordinary temperatures, the polystyrenes formed have comparatively low molecular weights. When the polymerization is slow the molecular weights of the products are much higher.

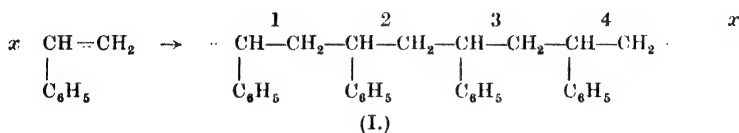
[1] Staudinger et al., *Ber.*, 1929, **62**, 241, 2912, 2921; Staudinger, *Die hochmolekularen organischen Verbindungen-Kautschuk und Cellulose*, Springer, Berlin, 1932.

[2] Whitby, *Trans. Faraday Soc.*, 1936, **32**, 315.

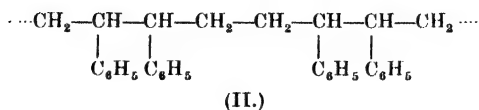
(*b*) *The Colloidal Nature of the Polystyrenes.*—The physical properties of the polymers vary with the length of the molecular chain. The polystyrenes and other vinyl polymers have been classified as hemicolloids, mesocolloids and eucolloids.[1] The hemicolloid polystyrenes have molecules containing 20 to 100 styrene units, corresponding to molecular weights from 2000 to 10,000. It is calculated that these molecules have lengths varying from 50 up to about 250 Å. The colloid properties of these relatively short molecules are not very pronounced. The solid material is either a powder or a gluey mass, which passes into solutions having low viscosities. The polystyrenes falling into the mesocolloid class are made up of molecules containing from 100 to about 1000 styrene units. The molecular weights and lengths being proportionately greater than those of the hemicolloids. The molecules of the eucolloids contain more than 1000 styrene units. The solid materials are tough and hard and have the characteristic properties of lyophilic colloids. On being dissolved the polymer swells to a marked extent, and the solutions are very viscous, even at low concentrations. The eucolloidal polystyrenes can be broken down by suitable treatment into shorter molecules having mesocolloidal and hemicolloidal properties.

(*c*) *The Structure of the Polystyrenes.*—As the unsaturation of the polystyrenes is small and, possibly, is confined to the terminal group, the transformation of styrene into polystyrene may be expressed in the following way (I.).

$$x\ \underset{\substack{|\\C_6H_5}}{CH}{=}CH_2 \rightarrow \cdots \overset{1}{\underset{\substack{|\\C_6H_5}}{CH}}{-}CH_2{-}\overset{2}{\underset{\substack{|\\C_6H_5}}{CH}}{-}CH_2{-}\overset{3}{\underset{\substack{|\\C_6H_5}}{CH}}{-}CH_2{-}\overset{4}{\underset{\substack{|\\C_6H_5}}{CH}}{-}CH_2 \cdots\ x$$

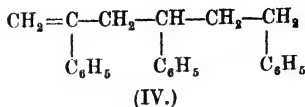
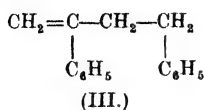
(I.)

This regular structure for polystyrene is preferred to an irregular arrangement of the styrene units such as (II.), because

$$\cdots CH_2{-}\underset{\substack{|\\C_6H_5}}{CH}{-}\underset{\substack{|\\C_6H_5}}{CH}{-}CH_2{-}CH_2{-}\underset{\substack{|\\C_6H_5}}{CH}{-}\underset{\substack{|\\C_6H_5}}{CH}{-}CH_2 \cdots$$

(II.)

[1] Staudinger, *Angewandte Chem.*, 1929, **42**, 69.

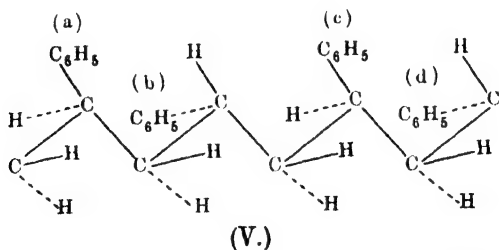
polystyrene on depolymerization yields some of the dimer and the trimer. The structures of these two compounds have been shown to be (III.) and (IV.).

$$CH_2{=}\underset{\substack{|\\ C_6H_5}}{C}{-}CH_2{-}\underset{\substack{|\\ C_6H_5}}{CH_2} \qquad\qquad CH_2{=}\underset{\substack{|\\ C_6H_5}}{C}{-}CH_2{-}\underset{\substack{|\\ C_6H_5}}{CH}{-}CH_2{-}\underset{\substack{|\\ C_6H_5}}{CH_2}$$

(III.) (IV.)

The regular structure is also in agreement with the optical properties of polystyrene, especially with the absorption spectrum, which resembles that of an alkyl benzene.[1] The nature of the end groups of the polystyrenes is not yet known.

It is generally agreed that the polystyrenes have chain or thread-like molecules. This gives a rough picture of the nature of the molecules, and it is permissible to speculate further on the fine structure of these polymers. Two free benzene nuclei will try to orient each other by means of van der Waal's forces, so that the rings are perpendicular to the line joining them.[2] This position, however, may change when the benzene nuclei are not entirely free to determine their mutual separations as in the polystyrene molecule.

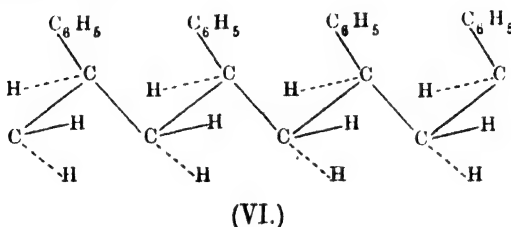
If it is assumed that the polystyrene molecular chain has a structure similar to that of the solid paraffins, the benzene nuclei may be disposed along this chain in two different ways. In the first arrangement the nuclei may be placed alternately above and below the plane of the carbon chain. This structure is indicated in the diagram (V.)

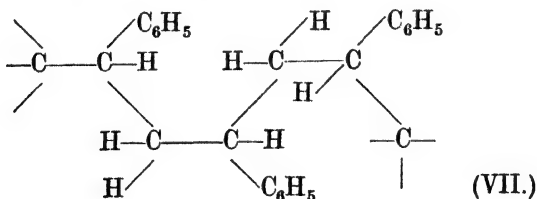
(V.)

[1] Staudinger and Steinhofer, *Annalen*, 1935, **517**, 35; de Boer, *Trans. Faraday Soc.*, 1936, **32**, 10; de Boer, Houwink, and Custers, *Rec. trav. chim.*, P.B., 1933, **52**, 799.

[2] de Boer, *Trans. Faraday Soc.*, 1936, **32**, 10; Fuller and Baker, *J. Chem. Educ.*, 1943, **20**, 3.

The nuclei marked (a) and (c) are above the plane of the carbon chain and those marked (b) and (d) are below the plane. In such an arrangement the adjacent benzene nuclei could lie perpendicular to the direction of the carbon chain, parallel to the direction of the chain, or one benzene nucleus could be perpendicular and one parallel. From considerations of the energy differences in these three positions, the first, in which the nuclei are perpendicular to the direction of the carbon chain, is to be preferred.

The second type of chain arrangement possible has all the benzene nuclei on the same side of the carbon chain. This can be represented as (VI.)

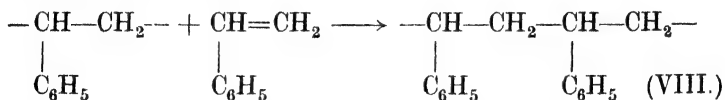
(VI.)

On the other hand, the polystyrene carbon chain may take up some other form when the benzene nuclei lie on the same side of the chain. For example, rotation of the groups could give rise to the configuration (VII.) in which the relatively large nuclei are separated in space from one another :

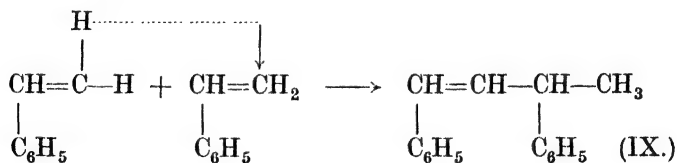
(VII.)

Here again energy contents point to the nuclei taking up positions perpendicular to the direction of the carbon chain. Finally it is possible that the polystyrene chain may take up a spiral form. It is to be expected that various configurations of the polystyrenes occur. There will, however, be common to all these configurations a tendency of the benzene nuclei to take up positions perpendicular to the carbon chain, or at least to oscillate about

equilibrium positions in which the nuclei are perpendicular to that direction.

(*d*) *The Mechanism of Polymerization*.—It has already been mentioned that the number of styrene units combined in one molecule of polystyrene varies with the conditions of polymerization. The simplest assumption is that the polymer molecule grows by the repeated addition of molecules of styrene to the chain. The process of molecular chain formation may be regarded as made up of three stages. First an initiation reaction, followed by a growth reaction and finally a termination reaction. If there is branching of the chains then another reaction must be added to these three, to account for the lateral growth.

The initiation reaction consists of an activation of the ethylenic linkage of the molecule. There are two possible ways of activating the unsaturated linkage; firstly a diradical may be formed (VIII.).

$$\underset{\displaystyle C_6H_5}{-\overset{|}{CH}}-CH_2- + \underset{\displaystyle C_6H_5}{\overset{|}{CH}}=CH_2 \longrightarrow -\underset{\displaystyle C_6H_5}{\overset{|}{CH}}-CH_2-\underset{\displaystyle C_6H_5}{\overset{|}{CH}}-CH_2- \quad \text{(VIII.)}$$

or secondly the energy of activation of the ethylenic linkage is reduced to such an extent that a molecule of monomer is capable of adding on to the excited linkage. This latter mechanism involves the transfer of a hydrogen atom to one side of the double bond and the rest of the addendum to the other (IX.).[1] The following scheme shows this.

$$\underset{\displaystyle C_6H_5}{CH}=\overset{\displaystyle H}{C}-H + \underset{\displaystyle C_6H_5}{CH}=CH_2 \longrightarrow \underset{\displaystyle C_6H_5}{CH}=CH-\underset{\displaystyle C_6H_5}{CH}-CH_3 \quad \text{(IX.)}$$

Growth of the molecule could then proceed by one or other of the mechanisms. Possibly both mechanisms play a part depending on the conditions of polymerization. With regard to the mechanism of the termination of the reaction, no definite conclusions have been reached. Large ring formation is regarded as unlikely.

[1] Whitby and Katz, *J. Amer. Chem. Soc.*, 1928, **50**, 1160; Whitby, *Trans. Faraday Soc.*, 1936, **32**, 315.

Apart from the presence of inhibitors in the polymerizing substance there are three ways in which termination of growth may occur. These are spontaneous loss of activity of the growing polymer, destruction of reactivity by collision with a molecule of monomer in some manner different from the type of collision by which the polymer grows, and thirdly the interaction of two active polymers in such a way as to lead to the mutual cancelling of their activity.[1]

(*e*) *The Molecular Weights of Polystyrenes.*—The ultra-centrifuge method of Svedberg gives the most reliable results in the determination of the molecular weights of polystyrenes. Three different fractions of polystyrenes in dilute solution in chloroform gave average values for the molecular weights of 30,000, 80,000, and 300,000. Other fractions have been examined and the molecular weights shown to vary from 5,000 to 1,000,000.[2]

Viscosity measurements may also be employed and give results in agreement with those obtained by the Svedberg sedimentation method.

2. *Polychloroprenes*

(*a*) *The Preparation of Chloroprene.*—In recent years β-chlorobutadiene (chloroprene), $CH_2{=}C(Cl){-}CH{=}CH_2$, and its polymerization products have been extensively examined.[3] The key to the preparation of chloroprene in a state of purity suitable for polymerization was the conversion of acetylene into monovinylacetylene. Acetylene under the catalytic influence of a saturated aqueous solution of cuprous and ammonium chlorides was converted into its polymers,

monovinylacetylene, $CH_2{=}CH{-}C{\equiv}CH$,

divinylacetylene, $CH_2{=}CH{-}C{\equiv}C{-}CH{=}CH_2$

and a compound with the molecular formula C_8H_8, which is believed to be 1 : 5 : 7-octatriene-3-ine,

$$CH_2{=}CH{-}C{\equiv}C{-}CH{=}CH{-}CH{=}CH_2.$$

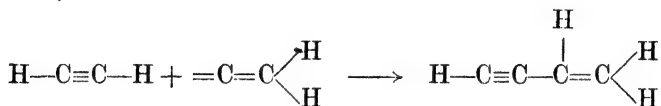
[1] Melville, *Trans. Faraday Soc.*, 1936, **32**, 258; Breitenbach, *Monatsh.*, 1938, **71**, 275.

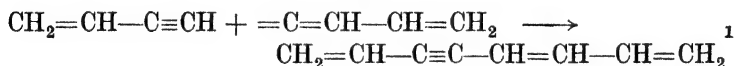
[2] Signer, *Z. physik Chemie*, [A], 1930, **150**, 257; 1933, **165**, 161; *Helv. Chim. Acta*, 1934, **17**, 59, 335, 726.

[3] Carothers, Williams, Collins, and Kirby, *J. Amer. Chem. Soc.*, 1931, **53**, 4203.

By suitable adjustments of the reaction conditions, the yield of monovinylacteylene could be substantially increased.

The mechanism of these polymerizations is not clearly understood, but it is thought probable that the first stage in the change is the formation of the complex from one or two molecules of acetylene and cuprous chloride; this product then undergoing a progressive reaction resulting, first, in the formation of monovinylacetylene, which then unites with another molecule of acetylene to yield the divinyl derivative. On the other hand, two molecules of monovinylacetylene may combine to form the compound C_8H_8. In these changes the acetylene molecules are pictured as being partly activated and existing in the form $=C=C\begin{smallmatrix}H\\H\end{smallmatrix}$, which react with normal acetylene to produce monovinylacetylene according to the following scheme,

$$H{-}C{\equiv}C{-}H + {=}C{=}C\begin{matrix}H\\H\end{matrix} \longrightarrow H{-}C{\equiv}C{-}\overset{H}{\overset{|}{C}}{=}C\begin{matrix}H\\H\end{matrix}$$

Similarly monovinylacetylene under the influence of the cuprous chloride is assumed to be activated and capable of reacting with normal monovinylacetylene to yield the end-product C_8H_8

$$CH_2{=}CH{-}C{\equiv}CH + {=}C{=}CH{-}CH{=}CH_2 \longrightarrow CH_2{=}CH{-}C{\equiv}C{-}CH{=}CH{-}CH{=}CH_2$$ [1]

Under other conditions monovinylacetylene yields 1 : 2-diacetylene*cyclo*butane or styrene.[2] The next stage was the conversion of monovinylacetylene into chloroprene. A mixture of monovinylacetylene, concentrated hydrochloric acid, cuprous chloride and ammonium chloride was shaken up for four hours at approximately 30° C. The oily material formed was washed, dried and distilled in vacuo, when chloroprene was obtained in 65 per cent. yield.[3]

(*b*) *The Polymerization of Chloroprene.*—When chloroprene was allowed to stand at 25° C. it gradually polymerized; after

[1] Nieuwland, Calcott, Downing, and Carter, *J. Amer. Chem. Soc.*, **1931**, **53**, 4197.

[2] Dykotra, *J. Amer. Chem. Soc.*, 1934, **56**, 1625.

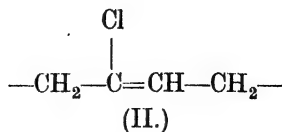
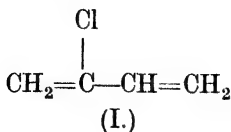
[3] Carothers et al., *loc. cit.*

twenty-four hours the viscosity of the liquid had considerably increased, and at the end of four days a stiff colourless, transparent jelly resulted. As polymerization proceeded further the jelly contracted in volume and became tougher, and at the end of ten days all the chloroprene had polymerized. The substance was now a colourless transparent elastic mass resembling a completely vulcanized soft rubber. This is known as μ-polychloroprene to distinguish it from other chloroprene polymers. It has the composition required for an addition polymer of chloroprene and is unsaturated. The chlorine atoms are very firmly bound in the molecule and apparently are still adjacent to ethylenic linkages, as only slight traces of chlorine are liberated when the substance is boiled in alcoholic potash. Oxidation of the μ-polymer with hot nitric acid yields some succinic acid.

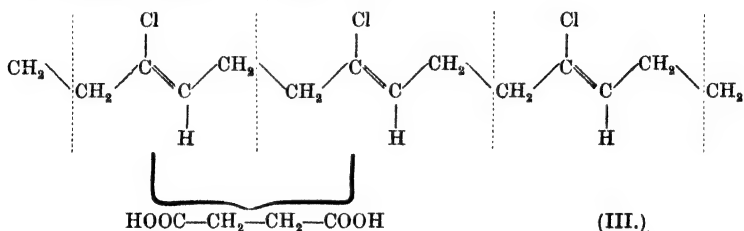
Oxygen is a powerful catalyst for the conversion of chloroprene into μ-polychloroprene. Thus at 25° C. in the presence of air chloroprene is polymerized to the extent of 90 per cent. in 8 days. In the absence of air this degree of polymerization is not reached until 400 days have passed. Peroxides also have a strong catalysing influence on the reaction. The effects of temperature, pressure and light are considerable. The μ-polymer is formed about four times faster at 65° C. than at 25° C.; at a pressure of 6,000 atmospheres the rate of polymerization was ten times greater than at ordinary pressure, and light of short wave lengths had marked accelerating effects on the transformation.

On the other hand, substances that generally act as anti-oxidants have a powerful inhibiting effect on the change from chloroprene into μ-polychloroprene. Phenol, quinones, amines, mercaptans, thiophenols, aromatic nitro-compounds and halogens all have greater or lesser inhibiting effects. An amount as small as 0·1 per cent. of catechol present in a sample of chloroprene prevented the formation of the final polymer over a period of several months.

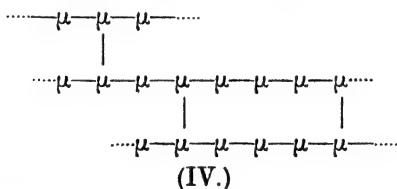
(c) *The Structure of μ-Polychloroprene.*—When a μ-polychloroprene is stretched about 500 per cent. it develops an X-ray diffraction pattern comparable with that of stretched natural rubber. It is consequently assumed that μ-polychloroprene has a molecular chain structure comparable with that assigned to natural rubber. The chain (III.) is built up from units (II.) derived from chloroprene (I.).

$$\underset{\text{(I.)}}{CH_2{=}\overset{\overset{\displaystyle Cl}{|}}{C}{-}CH{=}CH_2} \qquad \underset{\text{(II.)}}{{-}CH_2{-}\overset{\overset{\displaystyle Cl}{|}}{C}{=}CH{-}CH_2{-}}$$

From comparisons of the properties of natural rubber and μ-polychloroprene, and with those of synthetic isoprene rubbers it is concluded that there is considerable regularity in the arrangement of the units in the molecular chains of μ-polychloroprene. A *trans* configuration for the μ-polychloroprene chains is assumed as the dimensions of this shape agree best with the results of the X-ray analysis.* Accordingly the molecular chain of μ-polychloroprene may be represented as (III.).

$$CH_2 \diagdown CH_2 \diagup \overset{\overset{\displaystyle Cl}{|}}{C} \diagdown\!\!\diagdown \underset{\underset{\displaystyle H}{|}}{C} \diagup CH_2 \diagdown CH_2 \diagup \overset{\overset{\displaystyle Cl}{|}}{C} \diagdown\!\!\diagdown \underset{\underset{\displaystyle H}{|}}{C} \diagup CH_2 \diagdown CH_2 \diagup \overset{\overset{\displaystyle Cl}{|}}{C} \diagdown\!\!\diagdown \underset{\underset{\displaystyle H}{|}}{C} \diagup CH_2 \diagdown CH_2$$

$$HOOC{-}CH_2{-}CH_2{-}COOH \qquad \text{(III.)}$$

This structure accounts for the facts that oxidation yields succinic acid and that the chlorine atoms are resistant to the action of alkalis. As μ-polychloroprene, however, resembles vulcanized rubber, is not plastic and does not dissolve, but merely swells in rubber solvents, it is concluded that the molecular chains are chemically linked together at occasional points to form a three-dimensional structure. This may be represented by (IV.) in which " μ " stands for a chloroprene unit

```
······—μ—μ—μ—······
          |
·····μ—μ—μ—μ—μ—μ—μ—μ·····
             |         |
      ·····μ—μ—μ—μ—μ—μ—······
```

(IV.)

(*d*) *α-Polychloroprene.*—When chloroprene is allowed to stand under ordinary conditions in the presence of a little air, the polymer formed during the early stages of the reaction can be isolated by precipitation with alcohol or by distilling off

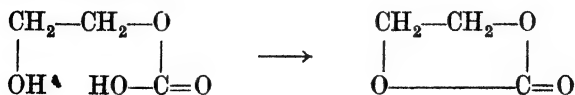
* Compare with formula for rubber, p. 211.

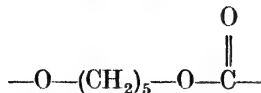
the unchanged chloroprene under diminished pressure. This polymer is soft, plastic and completely soluble in benzene. This substance is known as α-polychloroprene. When allowed to stand it is gradually transformed into a product apparently identical with the μ-polymer. From these facts it seems probable that the transformation of chloroprene into the μ-polymer is a step-wise reaction. The molecules of the α-polymer are assumed to have a linear structure of considerable length, and these are converted into the μ-compound by cross-linking to give a large three dimensional molecule of the type shown above (IV.).

(*e*) β-*Polychloroprene.*—When chloroprene is polymerized at about 60° C. in the presence of substances which inhibit the formation of μ-polychloroprene other polymers, known as β-polychloroprenes, are formed. The products of the reaction are volatile and can be separated by distillation into two fractions. They appear to be cyclic dimers of chloroprene and show no tendency to polymerize further. The polymerization of chloroprene can take still another course, leading to the ω-polymer. This is a coherent mass of glistening hard, rubbery granules or globules. It appears under diverse conditions, and it is possible that its formation is due to autocatalysis. The ω-polymer is non-plastic and shows scarcely any tendency to imbibe solvents. On this account it is assumed that there is a considerable amount of cross-linking in the molecular structure.

3. *Polyesters*

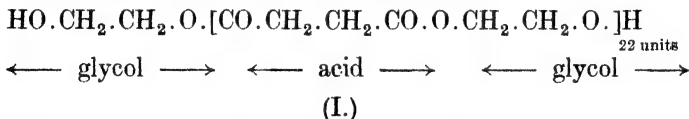
(*a*) *Preparation.*—Polyesters of high molecular weights are produced by the recurring condensation of acids and alcohols. For the condensation to take place there must be two suitable reacting groups in both the alcohol and the acid molecules, and, in addition, there must be little or no tendency to form five or six-membered cyclic compounds. The latter tendency may be avoided by selecting substances which, because of their molecular size, cannot form small ring derivatives. Thus a compound such as the carbonate of ethylene glycol is unsuitable for the production of the polyester as it could yield a five-membered ring compound as follows,

$$\begin{array}{ccc} CH_2\text{—}CH_2\text{—}O & & CH_2\text{—}CH_2\text{—}O \\ | \qquad\qquad | & \longrightarrow & | \qquad\qquad | \\ OH \quad HO\text{—}C{=}O & & O\text{————}C{=}O \end{array}$$

On the other hand, the reaction between methylene glycol and ethyl carbonate, which could give rise to an eight-membered ring, does not take this course but yields a polycondensate containing about twenty of the structural units,

$$—O—(CH_2)_5—O—\overset{\overset{\displaystyle O}{\|}}{C}—$$

in the molecule. The molecular weights of this substance varied from 2550 to 2840. In a similar way the products of the reaction between ethylene glycol and succinic acid, or between trimethylene glycol and adipic acid are polycondensates of high molecular weights. It is concluded from the methods of preparation and from their physical and chemical properties that these large condensates are in the form of linear molecules.[1] Taking the neutral ethylene succinate polycondensate, formed by the action of excess of ethylene glycol on succinic acid, as a typical example, it may be represented as (I.)

$$HO.CH_2.CH_2.O.[CO.CH_2.CH_2.CO.O.CH_2.CH_2.O.]_{22\ \text{units}}H$$

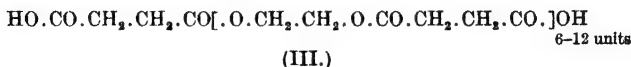
$$\longleftarrow \text{glycol} \longrightarrow \quad \longleftarrow \text{acid} \longrightarrow \quad \longleftarrow \text{glycol} \longrightarrow$$

(I.)

This substance reacts with *p*-bromobenzoic anhydride to yield a dibromobenzoyl derivative. The ester may be represented as (II.) and its formation furnishes evidence of the linear nature of the molecule

$$Br.C_6H_4.CO.O.CH_2.CH_2.O[.CO.CH_2.CH_2.CO.O.CH_2.CH_2.O.]CO.C_6H_4.Br \quad \text{(II.)}$$

When an excess of succinic acid is used in the condensation with ethylene glycol, the product has a molecular chain varying in length from six to twelve structural units and is acidic in character. This acidic polycondensate is considered to be (III.)

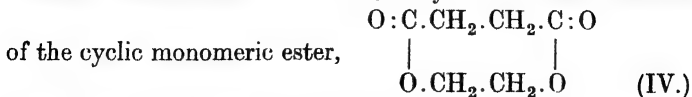
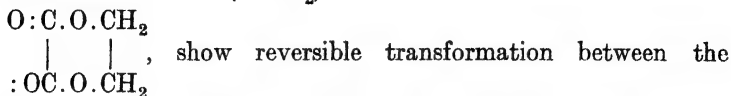
$$HO.CO.CH_2.CH_2.CO[.O.CH_2.CH_2.O.CO.CH_2.CH_2.CO.]_{6\text{–}12\ \text{units}}OH$$

(III.)

Prolonged heating of this material converts it into compounds of still higher molecular weights.

(*b*) *The Mechanism of the Reaction.*—The formation of an open chain polyester such as that represented in structure (I.)

[1] Meyer and Mark, *Der Aufbau der hochpolymeren organischen Naturstoffe*, Akademische Verlagsgesellschaft, Leipzig (1930).

might occur either, directly from the acid and the glycol by successive condensation reactions, or by the addition of molecules of the cyclic monomeric ester,

$$\begin{array}{l} O{:}C.CH_2.CH_2.C{:}O \\ | \qquad\qquad\qquad | \\ O.CH_2.CH_2.O \end{array} \qquad (IV.)$$

formed as an intermediate product. Although trimethylene carbonate, $O{:}C\left\langle\begin{array}{l}O.CH_2\\O.CH_2\end{array}\right\rangle CH_2$, and ethylene oxalate, $\begin{array}{l}O{:}C.O.CH_2\\ \;|\quad\;\; | \\ {:}OC.O.CH_2\end{array}$, show reversible transformation between the monomeric and polymeric forms, this type of change has not been detected in the reactions of the succinates and other esters which, in their cyclic monomeric forms, would have more than six atoms in the ring.[1] Further, the supposition that a cyclic monomeric ester is formed as an intermediate compound in the production of polysuccinates involves the tacit assumption that eight-membered rings are readily formed, and are unstable. This is contrary to the known facts. Such rings are produced only with great difficulty, and are stable once they are formed. As all attempts to isolate the monomeric ester (IV.) have failed, it is concluded that the long chains of the high polymers are built up by a series of successive condensation interactions of the succinic acid and glycol.[2]

4. *Polyamides*

When heated to above its melting point ε-aminocaproic acid reacts with itself, splitting off water to yield the simple lactam,

$$\begin{array}{l} CH_2.CH_2.CH_2.CH_2.CH_2 \\ \diagdown \qquad\qquad\qquad\quad | \\ H.N\text{———————}C{:}O \end{array}$$

and an undistillable material of approximately the same composition, having molecular weights varying from 800 to 1200. The lactam and the polyamide are readily separated by vacuum distillation or by extraction of the lactam with boiling alcohol. The polymer can be quantitatively hydrolyzed to the parent amino acid. Partial hydrolysis yields the tetrapeptide,

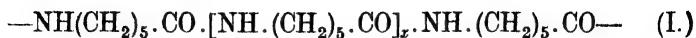
$$NH_2.(CH_2)_5.CO.NH.(CH_2)_5.CO.NH.(CH_2)_5.CO.NH.(CH_2)_5.COOH.$$

---

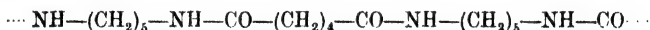
[1] Carothers and Van Natta, *J. Amer. Chem. Soc.*, 1930, **52**, 314.

[2] Carothers et al., *ibid.*, 1929, **51**, 2560; 1930, **52**, 711

Consequently the polymer may be represented as a chain molecule having the structure,

$$—NH(CH_2)_5.CO.[NH.(CH_2)_5.CO]_x.NH.(CH_2)_5.CO— \quad (I.)$$

The nature of the end groups has not yet been determined. It is a true condensation polymer formed directly from the amino acid by intermolecular reaction. This is evident from the fact that the lactam does not polymerize under the conditions of formation of the polyamide. As in the case of the polyesters, prolonged heating gives a new product. The change in properties after heating indicates a considerable increase in molecular weight.[1]

It has been found that mixtures of certain diamines and dicarboxylic acids also give polyamides of high molecular weight. For example, pentamethylene diamine, $NH_2—(CH_2)_5—NH_2$ and adipic acid, $HOOC—(CH_2)_4—COOH$ yield a polyamide of the type

$$\cdots NH—(CH_2)_5—NH—CO—(CH_2)_4—CO—NH—(CH_2)_5—NH—CO \cdots$$

The polyamides are of interest as some of them, known as nylons, yield artificial fibres of commercial importance. From the structure point of view it is interesting to compare these molecular structures with those assigned to silk and wool.*

[1] Carothers and Berchet, *J. Amer. Chem. Soc.*, 1930, **52**, 5289; Carothers and Hill, *ibid.*, 1932, **54**, 1566.

* For further information on this point the reader is referred to Astbury's very enlightening book, *Fundamentals of Fibre Structure.*

CHAPTER VIII

RUBBER

I. *Introductory*

THE exact distribution of credit among the pioneers in the chemistry of rubber produced a most unedifying amount of controversy [1]; and insinuations were made by at least one German chemist which appear to overstep the bounds of normal scientific polemics. In these circumstances, it seems desirable to give an outline of the history of the subject in its earlier stages.

In 1860 Williams [2] observed that when rubber is distilled it yields what are now known as isoprene and dipentene. On leaving isoprene in a partly-filled bottle for some months, he noticed that it became oxidized and was converted into a viscid liquid. When this viscid material was distilled, at one point in the process the liquid solidified to "a pure white spongy elastic mass" which, when burned, gave off the characteristic odour of burning rubber. The material in question, on analysis, yielded the following results: 78·8 per cent. carbon, 10·7 per cent. hydrogen, and 10·5 per cent. oxygen. This composition corresponds to isoprene plus half an atom of oxygen.

Bouchardat [3] in 1879 found that when hydrochloric acid solution is allowed to act upon isoprene, one of the products, after the reaction has proceeded for a fortnight or three weeks, is a non-volatile body having the composition C = 87·1 per cent., H = 11·7 per cent., and Cl = 1·7 per cent. If the chlorine be disregarded—and Bouchardat believed that its presence was due to contamination by foreign chlorinated compounds—these results agree closely with the formula $(C_5H_8)_x$. The substance

[1] For a complete account of this see Pond, *J. Amer. Chem. Soc.*, 1914, **36**, 165. See also Luff, *J. Soc. Chem. Ind.*, 1916, **35**, 983.

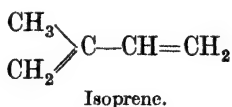
[2] Williams, *Phil. Trans.*, 1860, **160**, 245; *Proc. Roy. Soc.*, 1860, **10**, 516.

[3] Bouchardat, *Compt. rend.*, 1879, **89**, 1117.

thus produced "possesses the elasticity and other characteristics of rubber. It is insoluble in alcohol; it swells up in ether, also in carbon disulphide in which it dissolves in the manner of natural rubber." When submitted to dry distillation "it forms the same volatile hydrocarbons as rubber." "All these properties appear to identify this polymer of isoprene with the substances from which isoprene is formed, namely rubber."

Harries[1] in 1913, criticized this work of Bouchardat and attempted to prove that Bouchardat's method does not yield the products described. Unfortunately for his contentions, he had read the original paper so carelessly that he apparently attemped a repetition of the work by the employment of hydrochloric acid *gas* whereas Bouchardat used aqueous hydrochloric acid. When an attempt is made to repeat an author's work it is usual to employ his own method; not to try a new one and then declare that the described method "seems almost excluded." Harries also[2] asserted that Bouchardat had not proved the identity of his product with true rubber. It is difficult to see what more Bouchardat could have done, considering the date at which he worked; and this attitude in the critic becomes more astonishing when it is recalled that in 1910–11 Harries made use of tetrabromides, nitrosites, and ozonides as tests to distinguish rubber; but in 1912–13 he discarded these as being inefficient, and concentrated his attention upon the rate of decomposition of the ozonides with water.[3]

The next stage in the history of synthetic rubber is marked by Tilden's paper of 1882.[4] Tilden showed that when turpentine vapour is passed through a red-hot tube, isoprene

$$\begin{matrix} CH_3 \diagdown \\ \quad C{-}CH{=}CH_2 \\ CH_2 \diagup\!\!\diagup \end{matrix}$$

Isoprene.

is formed; and he also stated that, by the action of nitrosyl chloride, isoprene was converted into rubber. Ten years later, Tilden[5] made public the fact that some isoprene which had

[1] Harries, *Annalen*, 1913, **395**, 211.
[2] Harries, *Gummi-Zeitung*, 1910, **24**, 853.
[3] Harries, Lecture at Vienna, March 12, 1910; *Chem. Zeit.*, 1910, **34**, 316; *Annalen*, 1913, **395**, 211.
[4] Tilden, *Chem. News*, 1882, **46**, 220.
[5] Tilden, Paper read before the Philosophical Society of Birmingham, 1892.

been kept in a bottle for a long time had undergone change. "In place of the limpid colourless liquid the bottles contained a dense syrup in which were floating several large masses of solid, of a yellowish colour. Upon examination this turned out to be indiarubber." These original samples have now been tested by the ozone method and were found to be true rubber.[1] It may be noted that this work of Tilden's should be regarded as a real synthesis of rubber, and stands in a different category from Bouchardat's. Bouchardat obtained his isoprene by distilling rubber; so that his work consisted of *re-synthesizing* rubber from its decomposition products. Tilden, on the other hand, obtained his isoprene from turpentine, and may thus claim to have made a true synthesis of rubber.

Harries,[2] not having been able to repeat Tilden's work, contented himself with the statement that Tilden "never proved that he had rubber in his hands."

About 1899 or 1900, Kondakoff [3] showed that other members of the isoprene series could be converted into rubber-like materials by various methods.

In the earlier part of the present century, the uses of rubber were greatly extended; and as a natural consequence there was a marked effort to produce the material by artificial means on a manufacturing scale.

In 1909 Hofmann [4] discovered that isoprene may be converted into rubber by the action of heat. This is claimed as the first technical method of rubber synthesis. If it be a practical method it appears curious that, during the 1914–18 war, Germany was in great difficulties owing to lack of rubber.

In 1908 a British syndicate quietly set to work upon the problem of the commercial synthesis of rubber.[5] A method of obtaining isoprene from fusel oil was worked out, thereby ensuring that the raw material should not be too expensive. In the course of some experiments, it occurred to Matthews to

[1] Tilden, *Chemical Discovery and Invention in the Twentieth Century*, 1916; Pickles, *J.*, 1910, **97**, 1085.

[2] Harries, Vienna Lecture, 1910.

[3] Kondakoff, *On Synthetic Rubber* (in Russian) (1912); *J. pr. Chem.*, 1900, **62**, 175; 1901, **63**, 113; **64**, 109. See also Harries' Vienna Lecture and *Annalen*, 1911, **383**, 186.

[4] See Duisberg, *Eighth International Congress of Applied Chemistry*, 1912, **28**, 50, 86.

[5] See Perkin, *J. Soc. Chem. Ind.*, 1912, **31**, 616.

study the influence of sodium upon isoprene; and in July, 1910, he sealed the two substances up in a tube. Inspection of the tube in August showed that the contents had become viscid and contained a proportion of remarkably good rubber. The vessel was resealed and left till September, when it was found to contain a solid mass of amber-coloured rubber. A patent was applied for on October 25, 1910.

Meanwhile Harries, the Badische Anilin und Soda Fabrik, and Bayer and Co. were also at work, and the race was becoming a close one. Harries' story is as follows.[1] He claimed that in February, 1910, he observed, during a purification of isoprene by distilling it over sodium, that the metal had an "altering" (verändernde) action upon the hydrocarbon. The fact that rubber-like materials resulted from the process was first established "in September or October," which is rather vague. He stated that on October 28, 1910, he verbally communicated his discovery to a representative of the Elberfeld Farbenfabriken in Berlin, and suggested that a patent should be taken out by them. This patent was applied for in Germany on December 12, 1910, seven weeks after the British syndicate had applied for their English patent.*

If Harries' story be subjected to the same rigid scrutiny as he himself gave the work of Bouchardat and Tilden, the only evidence which could be regarded as relevant would be the actual date of the patent application, as no corroboration has been offered by the other details.† In any case, under modern conditions, priority of discovery counts for less than priority of publication; and on that basis the Germans lost the race.

The controversy which arose out of this defeat was marked by especial bitterness on the part of Harries [2]; and it is a matter for congratulation that chemical polemics are not usually conducted in that spirit.

[1] Harries, *Annalen*, 1912, **395**, 211.

* It appears that Aschan independently discovered the sodium polymerization process at a slightly later date. (See Aschan, *Naphtenverbindungen*, 1929, p. 321).

† The first scientific publication by Harries on the subject is dated June 26, 1911 (*Annalen*, **383**, 188), and he there stated (before the controversy arose) that he made the discovery at the *end* of 1910 (Ende des Jahres 1910).

[2] Harries, *Annalen*, 1912, **395**, 211.

2. *The Properties and Constitution of Natural Rubber*

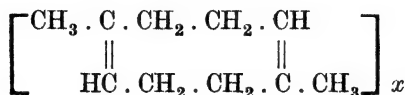
Natural rubber or caoutchouc is a transparent, tough elastic substance having no definite melting- or boiling-point.* It absorbs water, increasing in volume as it does so. It is soluble in several organic liquids, such as benzene, chloroform, carbon tetrachloride, dipentene, ligroin, and carbon disulphide. Its composition corresponds to the formula $(C_5H_8)_x$. It is unsaturated, combining readily with oxygen and chlorine; and it yields nitrosites and nitrosates with nitrous fumes. When distilled, it breaks down into a mixture of hydrocarbons of which the chief are isoprene and dipentene. When heated with sulphur or when treated with solutions of sulphur dichloride in carbon disulphide, it becomes "vulcanized," the process resulting in the rubber retaining its elastic properties over a wider range of temperature than when raw. When a high percentage of sulphur is introduced, vulcanite is produced.

Apart from the actions of halogens and nitrous fumes upon rubber, which have led to little, our knowledge of its constitution depends upon its behaviour with ozone.

Harries [1] stated that when rubber is treated with ozone and the resulting ozonide is decomposed with water, the only isolable products are laevulinic aldehyde, laevulinic acid, and the peroxide of laevulinic aldehyde. The acid is evidently a secondary product of reaction.

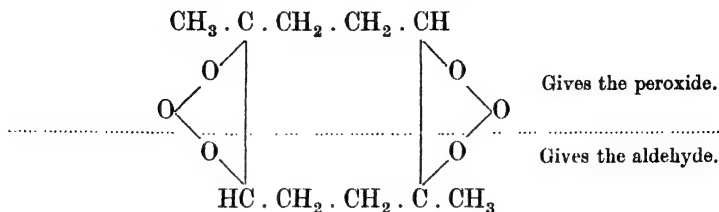
The molecular weight of the ozonide shows that its composition is $C_{10}H_{16}O_6$, which points to the fact that the structure from which it was derived must have contained two double bonds, each of which has taken up one molecule of ozone.

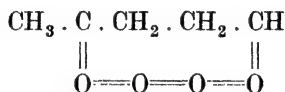
In order to account for these results, Harries had to resort to an hypothesis which will hardly recommend itself to many chemists. He assumed, from the production of laevulinic aldehyde and its peroxide, that rubber has the following structure:

$$\left[\begin{array}{l} CH_3 . \underset{\|}{C} . CH_2 . CH_2 . \underset{\|}{CH} \\ \quad\;\; HC . CH_2 . CH_2 . C . CH_3 \end{array}\right]_x$$

* It appears from some work of Harries that natural Para rubber occurs in at least three forms: oily, soluble, and insoluble.

[1] Harries, *Ber.*, 1905, **38**, 1195.

and that the ozonide has the constitution :

```
CH3 . C . CH2 . CH2 . CH
     /|              |\
   O  |              | O
  /   |              |  \
 O    |              |   O      Gives the peroxide.
..\...|..............|../.......................
   O  |              | O        Gives the aldehyde.
    \ |              |/
     HC . CH2 . CH2 . C . CH3
```

The breakdown of the ozonide is supposed to take place along the dotted line, the lower half of the molecule producing laevulinic aldehyde, $CH_3 . CO . CH_2 . CH_2 . CHO$, whilst the upper half yields the peroxide :—

```
CH3 . C . CH2 . CH2 . CH
      ||              ||
      O====O====O=====O
```

But at this point difficulties arise; for how can the *cyclo*-octadiene ring polymerize without destroying the double bonds in it? And if it does polymerize through the agency of the double bonds, how can they be left unchanged to attack the ozone molecules in order to produce the ozonide?

Harries endeavoured to gain credence for his hypothesis by adducing the fact that *cyclo*-octadiene—which should be analogous to his assumed eight-membered ring—does actually polymerize readily; but inadvertently, no doubt, he omitted to mention that one of the products of this polymerization is a di-*cyclo*-octadiene consisting of thin, pointed leaflets of m.p. 114° C.; whilst the other polymer is also a crystalline body.[1] The analogy with the properties of rubber is hardly close enough to support the eight-membered ring theory to any extent worth considering.

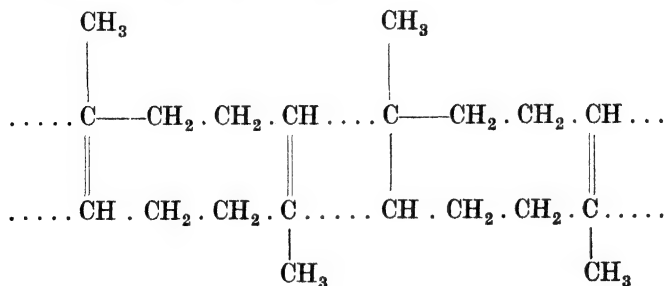
For his final demonstration of the presence of an eight-membered ring in the rubber molecule, Harries relied upon the following statements.[2] When the dihydrochloro-derivative of rubber is subjected to the action of pyridine,[3] he found that

[1] Willstätter and Veraguth, *Ber.*, 1905, **38**, 1975.
[2] Harries, *Ber.*, 1913, **47**, 2590.
[3] *Ibid.*, 733.

a substance *different* from rubber is regenerated.* On ozonizing this, he claimed to have isolated a *cyclo*-octadione derivative among the products. Therefore, according to his argument, the *original* rubber must have contained an eight-membered ring. The fallacy in reasoning is not worth dwelling upon, as it subsequently turned out [1] that he had made a "regrettable error" † and had mistaken an open-chain di-ketone

$$CH_3 . CO . CH_2 . CH_2 . CH_2 . CO . CH_3,$$

for a *cyclo*-octadione derivative. It seems hardly worth while to comment on the value of such evidence; though Harries still contended that it established the presence of an eight-membered ring in the rubber molecule.

Harries [2] proposed to regard the polymerization of the eight-membered rings as a mere kind of loose addition, so that the polymer breaks down into *cyclo*-octadiene molecules under the influence of ozone. In other words, he regarded rubber as being built up from a large number of separate *cyclo*-octadiene molecules clinging together by means of Thiele's partial valencies, somewhat in the following style :—

Pickles [3] has adduced several reasons why this conception should not be accepted without further evidence. In the first place, if ozone has the power of depolymerizing this peculiar compound, there seems no reason to deny the same depoly-

* "Dieser (the regenerated substance) ist nicht mehr identisch mit dem natürlichen Kautschuk."

[1] Harries, *Ber.*, 1914, **48**, 784.

† "Ein bedauerlicher Irrtum."

[2] Harries, *Ber.*, 1905, **38**, 1195, 3985.

[3] Pickles, *J.*, 1910, **97**, 1085.

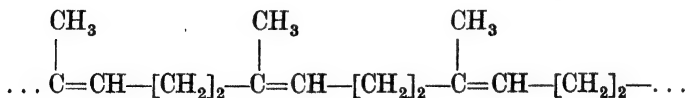
merizing property to other reagents. On this basis, bromine would first break down the colloidal rubber to independent *cyclo*-octadiene derivatives which would then yield a simple tetra-bromo-compound, $C_{10}H_{16}Br_4$; but in actual practice the bromo-derivative of rubber appears to be almost as complex as rubber itself.*

Again, nitrous fumes might be expected to resemble ozone in their effects; but their action on rubber, as studied by Harries himself, produces complicated substances with compositions,† established by molecular weight determinations, corresponding to $C_{20}H_{30}O_{14}N_6$ and even $C_{40}H_{62}O_{24}N_{10}$.

Yet another objection to the physical polymerization idea is to be found in the behaviour of rubber when heated. Under ordinary pressure, heated rubber shows exactly the phenomena ordinarily observed when a complex substance undergoes complete disruption; whilst if the heating be done under reduced pressure, *cyclo*-octadiene derivatives are not formed, but instead it is found that the simplest compound in the distillate contains at least twenty carbon atoms.‡

This does not exhaust the evidence against Harries' idea; but it is sufficient to indicate some of the weak points of his hypothesis.

Pickles proposed a formula which certainly avoids these difficulties. He suggested that rubber consists of long chains built up from the group C_5H_8 by normal polymerization :—

$$\ldots \underset{\displaystyle}{\overset{\displaystyle CH_3}{\overset{|}{C}}}{=}CH{-}[CH_2]_2{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH{-}[CH_2]_2{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH{-}[CH_2]_2{-}\ldots$$

The oxidation results require that the two ends of the chain should be linked together; and Pickles assumed that at least eight C_5H_8 complexes are included in a ring. To account for the ozone results, Pickles proposed the hypothesis that after

* Harries (*Annalen*, 1911, **383**, 227) endeavoured to get round this by suggesting that the bromo-derivative is an adsorption compound, an hypothesis for which he adduced no evidence.

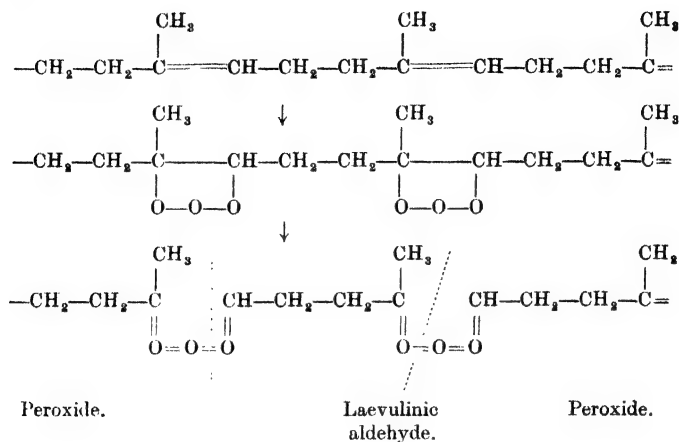
† Harries (*Annalen*, 1911, **383**, 227) asserted, in reply to this, that most terpene nitrosites are bimolecular, which would reduce the rubber nitrosite to $C_{10}H_{15}O_7N_3$, thus making the C_8 ring possible.

‡ Harries made no reply to this argument.

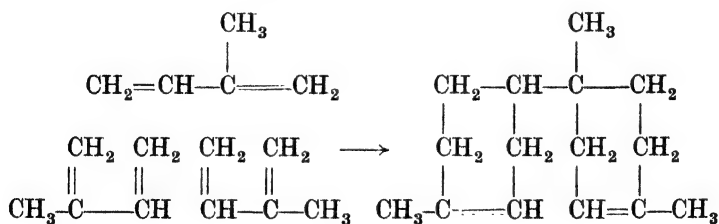
the formation of the ozonide, the linkage between the carbon atoms is ruptured whilst the ozonide chain remains intact till later :—

```
            CH3                        CH3                        CH3
             |                          |                          |
—CH2—CH2—C═══════CH—CH2—CH2—C═══════CH—CH2—CH2—C=

            CH3          ↓             CH3                        CH3
             |                          |                          |
—CH2—CH2—C──────────CH—CH2—CH2—C──────────CH—CH2—CH2—C=
             |          |               |          |
            O—O—O                     O—O—O
                         ↓
            CH3                        CH3                        CH3
             |                          |                          |
—CH2—CH2—C        CH—CH2—CH2—C        CH—CH2—CH2—C=
             ‖          ‖               ‖          ‖
            O=O=O                     O=O=O

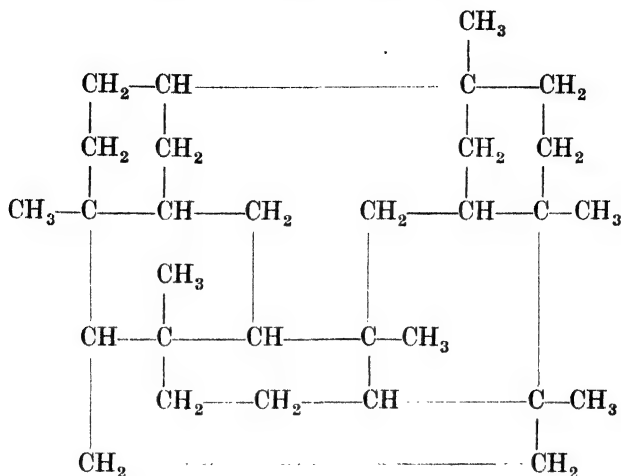
   Peroxide.                Laevulinic            Peroxide.
                             aldehyde.
```

This proposal certainly throws less strain upon the chemist's credulity than is demanded by Harries' hypothesis; and it appears to be supported by the work of Ostromisslenski.[1]

Another view of rubber's constitution is due to Boswell.[2] He assumed that three molecules of isoprene combine to form a cyclic compound, $C_{15}H_{24}$, containing two double bonds :—

```
              CH3                                 CH3
               |                                   |
      CH2=CH—C═══CH2                    CH2—CH—C——CH2
                                          |    |    |    |
   CH2   CH2   CH2   CH2      ——→      CH2  CH2  CH2  CH2
   ‖     ‖     ‖     ‖                   |    |    |    |
CH3-C————CH    CH—C—CH3             CH3-C————CH   CH=C—CH3
```

In virtue of its two ethylenic linkages, this substance is assumed to enter into combination with further molecules of isoprene, yielding structures like the following :—

[1] Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1932.

[2] Boswell, *Canadian Chemistry and Metallurgy*, 1922, **6**, 238; *Trans. Roy. Soc. Canada*, 1922, **16**, iii, 27.

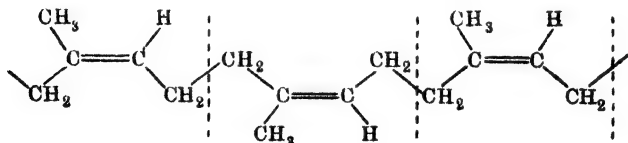
```
                                              CH3
                                              |
        CH2—CH ------------------------------ C———CH2
        |   |                                 |    |
        CH2 CH2                               CH2  CH2
        |   |                                 |    |
   CH3—C———CH———CH2          CH2———CH———C—CH3
       |            |          |            |
       |    CH3     |          |            |
       |    |       |          |            |
       CH———C———————CH—————————C—CH3        |
            |                  |            |
       |    CH2———CH2—————————CH -----------C—CH3
       |                                    |
       CH2 ---------------------------------CH2
```

which is assumed to be the structure of the rubber molecule. In support of this hypothesis, the following evidence can be quoted. By the action of hydrogen peroxide or potassium permanganate upon rubber, Boswell obtained a derivative $C_{25}H_{40}O_2$, which he believed to be formed by the loss of the central C_5H_8 group from the rubber molecule formulated above and its replacement by two oxygen atoms. By the action of hydrogen peroxide on rubber, a second oxidation product, $C_{15}H_{24}O$, was isolated, which Boswell assumed to result from further oxidation of the compound $C_{25}H_{40}O_2$ during which two more isoprene groups are eliminated. When oxidized by air, rubber was found to yield a highly-oxygenated derivative, $C_{25}H_{40}O_2$, wherein, on Boswell's view, the five isoprene groups are connected by oxygen atoms. After this, any further oxidation produces rupture of the molecule. The action of iodine on rubber is peculiar in that when iodine alone is used, the reaction is slow; but in presence of oxygen it is rapid; and it yields a compound $C_{25}H_{40}O_9$, if hydrogen peroxide be employed along with the iodine. It was suggested by Boswell that the iodine atom served to link together various isoprene nuclei within the molecule.

The main disadvantage of Boswell's formula is that it fails to make clear the action of ozone upon the rubber molecule. To get over this difficulty, he assumed that the first action of ozone is a depolymerizing one and that the ozonide is formed after a

rearrangement of the five isoprene nuclei thus produced. Boswell points out, however, that the ozone method does not give a quantitative yield of ozonide from rubber nor does it even produce a constant quantity of ozonide from a given amount of rubber.[1] It is therefore by no means certain that Harries' ozonide is a homogeneous material and the sole product of the ozonization of rubber. Obviously this throws still further doubt upon Harries' view of the constitution of rubber.

Katz [2] discovered by X-ray examination that when rubber is stretched it develops a strongly marked crystalline structure, which disappears on the release of the tension or on heating the material. Thus in the unstretched state, rubber is apparently amorphous; but on extension it yields an X-ray photograph rather like that given by asbestos. The structure of the stretched material appears to be built up from a series of crystallites which are all oriented in such a way that a certain crystallographic axis points in the direction of the tension.[3] The possibility of a crystal unit containing four C_5H_8 groups has been inferred from the measurements.

This and other properties of rubber can be explained by assuming that the molecules exist in long chains of isoprene units linked with the methylene groups in the *cis*-position to one another. This is represented as follows:

```
   CH3        H     :                   :  CH3       H     :
     \       /      :                   :    \      /      :
      C====C        : CH2          CH2  :     C====C       :
     /       \      :/    \        /    :    /      \      :/
 \CH2         CH2   :      C====C       :CH2         CH2   :
                    :     /      \      :                  :
                    :  CH3        H     :                  :
```

The elasticity of rubber is attributed to a molecular change of shape: in the unstretched material the molecular chains are in a folded or helical condition. When the rubber is stretched the chains unfold and become extended, returning to the folded condition when the stretching tension is removed.[4] The "molecular" weight of rubber in different solvents determined by

[1] Olivier, *Rec. trav. chim.*, 1921, **40**, 665.

[2] Katz, *Kolloid-Z.*, 1925, **36**, 300.

[3] Hauser and Mak, *Koll. Chem. Beih.*, 1926, **23**, 64; Hauser, *Ind. Eng. Chem.*, 1929, **21**, 249.

[4] Meyer and Mark, *Ber.*, 1928, **61**, 1939; Fickentscher and Mark, *Kolloid-Z.*, 1929, **49**, 135; Simard and Warren, *J. Amer. Chem. Soc.*, 1936, **58**, 507.

osmotic pressure, viscosity and sedimentation measurements varied from 150,000 to almost 400,000.[1]

3. *The Anglo-French Synthesis of Rubber*

In devising a manufacturing process on a large scale, the first point to be considered is the possible supply and price of the raw material involved.[2] A synthesis of rubber on a commercial scale might imply a demand running up to 100,000 tons; and before proceeding further it is necessary to make sure that this demand can be filled without producing a shortage in the raw material.

Turpentine appeared at first sight to be a suitable starting-point; but the imports of that substance into this country in the years previous to 1910 were found to average less than 29,000 tons per annum; so that the additional demand for three times that quantity would disturb the market and cause a rise in price which it would be difficult to estimate. Acetone was also ruled out by the question of cost; since, in order to compete with natural rubber, the artificial substitute must be manufactured at a price not exceeding one shilling per pound.*

The choice of the syndicate fell upon starch, which was readily obtainable at a low price. An alliance was made with Fernbach, of the Pasteur Institute; and this investigator worked out a fermentation process whereby starch (from maize or potatoes) is convertible into fusel oil by one method and into acetone by another. The fusel oil thus obtained was found to contain an exceptionally high percentage of butyl alcohol.

The next stage in the process consists in treating butyl alcohol with hydrochloric acid gas, whereby it is converted into butyl chloride.

By the action of chlorine, a mixture of dichloro-derivatives is obtained from the butyl chloride; and an apparatus was

[1] Meyer and Mark, *ibid.*; Staudinger and Nodzu, *Ber.*, 1930, **63**, 721; Lansing and Kraemer, *J. Amer. Chem. Soc.*, 1935, **57**, 1369.

[2] For a complete account of the history of the syndicate's work, see Perkin, *J. Soc. Chem. Ind.*, 1912, **31**, 616.

* These figures refer, of course, to pre-1914 prices.

devised which checked the formation of more highly halogenated compounds. The final product contains a mixture of 1,2-, 1,3- and 1,4- dichlorobutane.

Contrary to what might have been expected, these substances, when passed over heated soda-lime, all give rise to the same product: butadiene: $CH_2 : CH . CH : CH_2$. Apparently intramolecular change takes place in the case of 1,2-dichlorobutane, or its product, under the influence of the soda-lime.

The final stage, conversion of the butadiene into artificial rubber, is carried out by allowing the hydrocarbon to stand in contact with a small quantity of sodium, the length of time required ranging from hours to weeks and being dependent upon temperature conditions.

Another method of obtaining artificial rubber has been suggested by Perkin, starting from amyl alcohol. The alcohol is converted into amyl chloride; the latter is then chlorinated, as in the case of butyl alcohol, producing a series of dichloro-derivatives which, when passed over heated soda-lime, yield isoprene. By treatment with metallic sodium, the isoprene polymerizes to an artificial rubber which is different in constitution from the butadiene rubber.

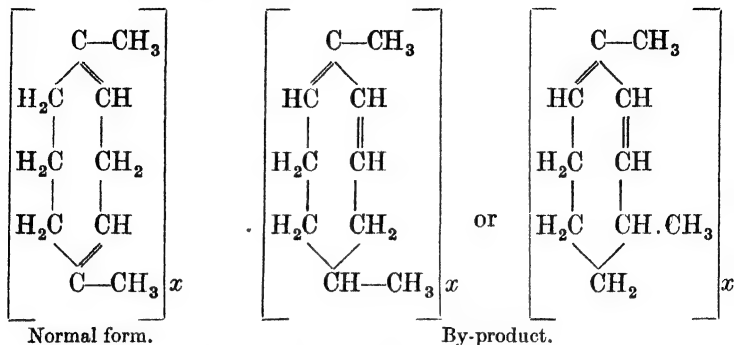
4. *Natural Rubber and the Artificial Rubbers*

It must be clearly borne in mind that the synthetic rubbers, though they have many resemblances to natural rubber, are not identical with it in chemical constitution. Some of them, as is evident from their raw materials, are obviously different; whilst even in the case of isoprene polymers we cannot safely assert that their identity with natural rubber is proved.[1]

Harries [2] stated that the autopolymerization of isoprene gives rise in the main to what he called a "normal" product; but that along with this is formed, in small yield, a different substance, on his ring-hypothesis, the formulae of these bodies are shown below :—

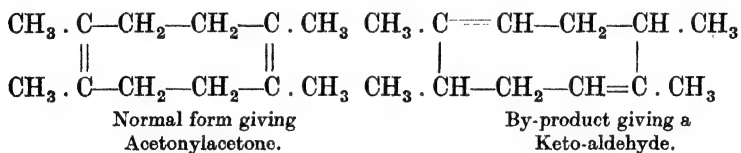
[1] Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1916, **48**, 1071.
[2] Harries, *Annalen*, 1911, **383**, 184.

$$\left[\begin{array}{ccc} & C{-}CH_3 & \\ & \diagup \;\; \diagdown\!\!\diagdown & \\ H_2C & & CH \\ | & & | \\ H_2C & & CH_2 \\ | & & | \\ H_2C & & CH \\ & \diagdown \;\; \diagup\!\!\diagup & \\ & C{-}CH_3 & \end{array}\right]_x \qquad \left[\begin{array}{ccc} & C{-}CH_3 & \\ & \diagup\!\!\diagup \;\; \diagdown & \\ HC & & CH \\ | & & \| \\ H_2C & & CH \\ | & & | \\ H_2C & & CH_2 \\ & \diagdown \;\; \diagup & \\ & CH{-}CH_3 & \end{array}\right]_x \text{ or } \left[\begin{array}{ccc} & C{-}CH_3 & \\ & \diagup\!\!\diagup \;\; \diagdown & \\ HC & & CH \\ | & & \| \\ H_2C & & CH \\ | & & | \\ H_2C & & CH.CH_3 \\ & \diagdown \;\; \diagup & \\ & CH_2 & \end{array}\right]_x$$

Normal form. By-product.

The proof adduced in favour of the by-product structure was that he thought he isolated methyl-glyoxal among the decomposition products of the ozonide.*

In the case of the polymer of dimethyl-butadiene, two ozonides were obtained which, on decomposition, yielded acetonylacetone and some strong reducing substances. From this Harries deduced that along with the "normal" polymer in this case there must be produced another which yields the reducing material, assumed by him to be a keto-aldehyde. For the two forms which he believed to exist he devised the following formulae which may possibly be established when any definite evidence in their support is produced :—

$$\begin{array}{l} CH_3 . \underset{\|}{C}{-}CH_2{-}CH_2{-}\underset{\|}{C} . CH_3 \\ CH_3 . C{-}CH_2{-}CH_2{-}C . CH_3 \end{array} \qquad \begin{array}{l} CH_3 . \underset{|}{C}{=}CH{-}CH_2{-}\underset{|}{CH} . CH_3 \\ CH_3 . CH{-}CH_2{-}CH{=}C . CH_3 \end{array}$$

Normal form giving Acetonylacetone. By-product giving a Keto-aldehyde.

Further results were given in a later paper.[1] An examination of the rate of decomposition of various ozonides was carried out by the following method. About 10 grammes of the ozonide were suspended in 100 grammes of water and heated under a reflux to 120°–125° C. Every quarter (or half) hour the mixture was shaken until the ozonide stuck to the walls of the vessel; the clear liquid was then poured off; the vessel and ozonide were dried for some hours *in vacuo* and then weighed: the decanted liquid was poured back and a fresh experiment begun.

* "Unter diesen wurde ein Produkt festgestellt, welches ich für Methylglyoxal ansprechen möchte."

[1] Harries, *Annalen*, 1912, **395**, 211.

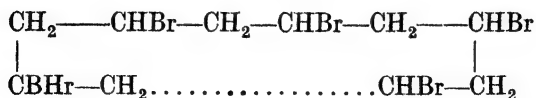
From the loss of weight in the ozonide the amount of decomposition was calculated.

Harries stated that the rates of ozonide decomposition were similar for natural rubber and for autopolymerized isoprene. Divergency was noted in the case of a rubber obtained from piperylene, $CH_3 . CH : CH . CH : CH_2$, which is not astonishing in view of the fact that piperylene-rubber gives ozonide decomposition products differing entirely from those of natural rubber.

The decomposition curves of the ozonides derived from the rubbers obtained by the sodium-polymerization process differ, according to Harries, from the curve for the ozonide of natural rubber; but it must be noted that he himself pointed out that even natural rubbers differ among themselves in the readiness with which they form ozonides.

The same method was applied to synthetic 1 : 5-*cyclo*-octadiene; and Harries stated that its ozonide breaks down at almost exactly the same rate as the ozonide of butadiene-rubber. From this he claimed to have proved that his eight-membered ring hypothesis is correct; but it appears that if Pickles' postulates as to the structure of the ozonide were applied to this case the argument for his formula would hold just as well.

Ostromisslenski [1] obtained by the polymerization of vinyl bromide a material which he termed caouprene bromide. This exists in three forms $\alpha \rightarrow \beta \rightarrow \gamma$ which, when submitted to the action of ultra-violet light, are capable of change in the direction shown by the arrows. Boiling with anhydrous acetic acid has a similar effect. The bromide of Harries' butadiene-rubber, which also exists in three modifications, is either identical or isomeric with caouprene bromide. Ostromisslenski did not accept Harries' eight-membered ring hypothesis, but regarded caouprene bromide as constituted in the following manner :—

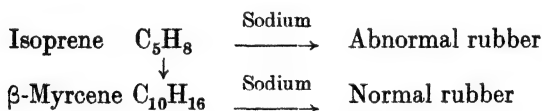
$$\begin{array}{l} CH_2\text{——}CHBr\text{—}CH_2\text{—}CHBr\text{—}CH_2\text{——}CHBr \\ | \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad | \\ CBHr\text{—}CH_2 \ldots\ldots\ldots\ldots\ldots\ldots CHBr\text{—}CH_2 \end{array}$$

where the dotted line represents an unknown number of $—CH_2.CHBr—$ groups. Both caouprene bromide and butadiene-rubber bromide, when treated with zinc dust, yield the same rubber, apparently butadiene-rubber.

[1] Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1912, **44**, 204.

The work of Ostromisslenski[1] has been so fertile in this field that it seems regrettable that his papers are published in a language which few British chemists can read. He apparently made a very complete investigation of the methods of preparing butadiene, no fewer than twenty-nine of these being described in a single paper.

Ostromisslenski differed from Harries with regard to the classification of the rubber-like materials produced by synthetic methods. In his view, the physical properties of the product are better indices of its nature than the results of decomposition-reactions have proved to be. For example, a determination may be made of the temperatures at which an artificial rubber acquires and loses its elastic properties; and if these temperatures agree approximately with those for natural rubber, Ostromisslenski considered that the synthetical substance is "normal." If, on the other hand, there is little agreement here and if the range of temperature over which the artificial product remains elastic is different from the range found for natural rubber, then the artificial product should be regarded as "abnormal."

The complexity of the process whereby synthetic rubbers are formed is well illustrated by some of Ostromisslenski's results. When isoprene is kept at a temperature of 80°–90°, it forms an open-chain dimeric form named β-myrcene. This substance, on polymerization by the sodium process, yields a "normal" rubber; whereas isoprene itself, when treated with sodium, gives rise to an "abnormal" polymer.

$$\begin{array}{lcl} \text{Isoprene } C_5H_8 & \xrightarrow{\text{Sodium}} & \text{Abnormal rubber} \\ \quad\downarrow & & \\ \beta\text{-Myrcene } C_{10}H_{16} & \xrightarrow{\text{Sodium}} & \text{Normal rubber} \end{array}$$

Further variation seems to be induced by the presence of carbon dioxide. If the sodium polymerization be conducted in a carbon dioxide atmosphere, the end-product is a type of rubber differing from that obtained in the normal sodium process since it is less easily dissolved in or attacked by benzene.[2]

Lebedeff[3] investigated the polymerization of divinyl derivatives containing conjugated double bonds. The reaction

[1] Ostromisslemski, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1374, 1472, 1494, 1507, 1928, 1932, 1937, 1941.

[2] Holt, *Z. angew. Chem.*, 1914, **27**, 156.

[3] Lebedeff, *J. Russ. Phys. Chem. Soc.*, 1910, **42**, 949; 1911, **43**, 820.

products contain cyclohexene compounds as well as a resinous material derived from cyclo-octadiene. Low temperatures and the action of light favour the formation of the *cyclo*-octadiene compounds: while *cyclo*hexene derivatives are produced at higher temperatures. Substances of the allene type give rise to *cyclo*butane compounds.

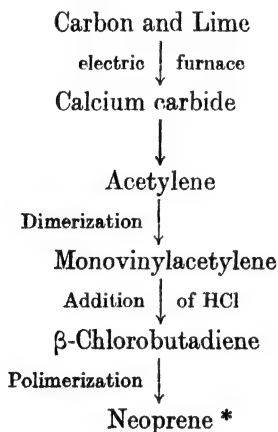
In recent years a number of synthetic rubber-like substances have been produced and are now being manufactured on a large scale. Some of these substances have very low solubilities in mineral and vegetable oils, others have a marked resistance to atmospheric oxidation, light, heat and abrasion. Such properties make the synthetic materials more useful than natural rubber for certain purposes. The principal synthetic substances are chlorinated rubber and polymers of chloroprene (β-chlorobutadiene), butadiene, vinyl chloride and organic sulphides.

Chlorinated rubber, strictly speaking, is not a synthetic substance as natural rubber is the raw material used. The establishment of the rubber plantation industry was largely due to British enterprise and capital, and consequently it was to be expected that strenuous attempts would be made in this country to modify natural rubber to meet the many needs of modern industry. Chlorinated rubber was developed in Britain and is now manufactured in most of the large countries of the world. Early attempts were made to chlorinate sheet rubber. Later the chlorination (of rubber) in solvents such as carbon bisulphide, chloroform and carbon tetrachloride was found to be more effective. One of the earliest attempts to chlorinate rubber in solution showed that when a one per cent. solution of rubber in chloroform was used, hydrogen chloride was evolved and the end-product contained about sixty-five per cent. of chlorine.[1] This indicated that substitution had taken place as well as addition, and the method is the basis of the present-day practice. Carbon tetrachloride is now largely used as the solvent, and by controlling the amount of chlorine absorbed as well as the temperature and pressure, materials of different properties may be obtained. Cheaper solvents such as benzene may be employed if precautions are taken to exclude substances which act as catalysts for the interaction of benzene and chlorine.[2]

[1] Gladstone and Hibbert, *J.*, 1888, 53, 679.

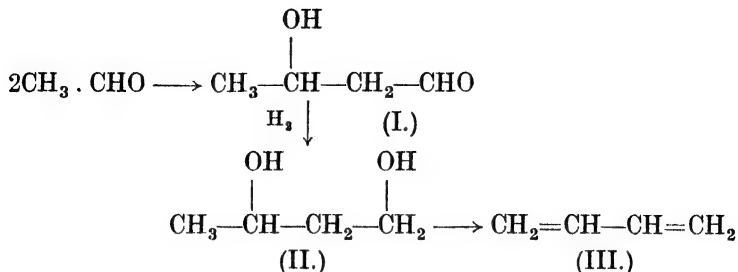
[2] Broadhurst, Lamble, Peachey, and United Alkali Co., B.P. 127481, 1919.

Chlorinated rubbers find their chief outlet in the paint and lacquer industries and are known in this country by the trade names Alloprene and Detel. The chlorinated rubbers are chemically inert, acids and alkalis have very little effect on them and intense heat produces only local charring.

Polymerized β-chlorobutadiene, known as neoprene, has been developed in the Unites States of America. The materials, lime, carbon and hydrogen chloride, for the production of neoprene are cheap and readily available, but at present yields at different stages in the process are such that the cost of the synthetic material is considerably higher than that of natural rubber. The following diagram shows the steps in the synthesis of neoprene,

The synthetic rubber-like substances obtained by the polymerization of butadiene have been developed principally in Russia and Germany. Three principal raw materials are used in the large-scale production of butadiene; these are acetylene (Germany), ethyl alcohol (Russia) and petroleum and petroleum gases (U.S.A.). Acetylene may be converted into butadiene by conversion into monovinylacetylene and reduction of the acetylenic bond to an ethylenic one, or the acetylene may be converted into acetaldehyde, which by condensation yields the aldol (I.). This compound on reduction is transformed into butylene glycol (II.), which on dehydration passes into butadiene (III.):

* See Chapter VII.

$$
2CH_3.CHO \longrightarrow CH_3\text{—}\underset{}{\overset{OH}{\overset{|}{C}}}H\text{—}CH_2\text{—}CHO \quad (I.)
$$

$$
\xrightarrow{H_2} CH_3\text{—}\overset{OH}{\overset{|}{C}}H\text{—}CH_2\text{—}\overset{OH}{\overset{|}{C}}H_2 \ (II.) \longrightarrow CH_2{=}CH\text{—}CH{=}CH_2 \ (III.)
$$

When 85–90 per cent. ethyl alcohol is heated to a high temperature in the presence of a dehydrating catalyst, such as alumina, butadiene is obtained in about 30 per cent. yield. The crude material is washed and distilled bringing its concentration of butadiene up to about 80 per cent. This material is polymerized by sodium in an atmosphere of nitrogen in an autoclave. The temperature is controlled at 30° C. for two hours and gradually raised to 60° C. and eight atmospheres pressure. Polymerization is complete in thirty-six hours.[1] Sodium is not the ideal polymerizing agent for butadiene and many other catalysts have been tried and such substances as diazoaminobenzene and acetoacetic ester have been found satisfactory.[2] A further advance was made when the technique of polymerization in aqueous solution was developed. One method consists in the use of an emulsifying agent of the modified higher aliphatic alcohol type and allowing the polymerization to proceed at a *p*H below 7.[3] For example, 20 parts of the emulsifying agent were dissolved in 200 parts of water, 0·15 part of ammonium persulphate, and 3·5 parts of normal acetic acid, 75 parts of butadiene and 25 parts of styrene were added and the whole emulsified. The emulsion was shaken for several days at 30° C. and yielded a good quality mixed butadiene-styrene polymer. This practice of allowing the polymerization of butadiene to take place in the presence of another polymerizing substance has great possibilities, and both styrene and acrylic nitrile are being successfully used in this way. The proportion of styrene or nitrile present in the mixture may be varied within certain limits

[1] Nebovidsky, *Bull. Assn. Chim.*, 1938, **55**, 215; Zavalkov, *Sintel-Kauchuk*, 1934, **2**, 15.

[2] Buizov, *J. Appl. Chem. Russia*, 1933, **6**, 1074; For. Petrol. Tech., 1934, **2**, 194.

[3] I. G. Farbenindustrie A.-G., E.P., 521277, May 16, 1940.

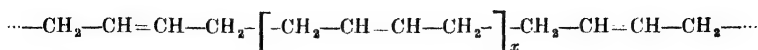
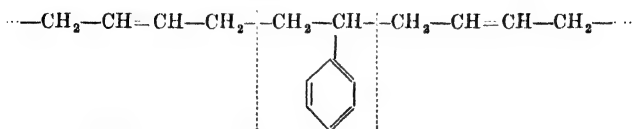
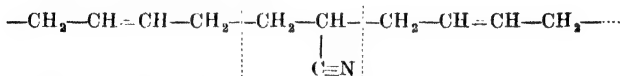
and " rubbers " with varying properties obtained. The structures of the butadiene polymers may be formulated as long chains and cross-linkages between chains could give rise to more complex aggregates.

$$\cdots—CH_2—CH=CH—CH_2-\left[-CH_2—CH=CH—CH_2-\right]_x-CH_2—CH=CH—CH_2—\cdots$$

Pure butadiene polymer

$$\cdots—CH_2—CH=CH—CH_2-\vdots-CH_2—CH(C_6H_5)-\vdots-CH_2—CH=CH—CH_2—\cdots$$

Butadiene-styrene polymer

$$—CH_2—CH=CH—CH_2-\vdots-CH_2—CH(C{\equiv}N)-\vdots-CH_2—CH=CH—CH_2—\cdots$$

Butadiene-acrylic nitrile polymer.

In Germany these polymers are known as Buna and Perbunan " rubbers." The substances briefly described here are a few of the industrial products. It is apparent from the intensive research work being carried on and the rapid progress being made in the development of synthetic rubber-like substances that many further products having properties suitable for special purposes will become available in the near future.

CHAPTER IX

SOME DEUTERO-ORGANIC COMPOUNDS

1. *Introductory*

An indication of the existence of a heavy isotope of hydrogen was first obtained when the atomic weight of hydrogen relative to oxygen, determined by Aston's mass spectrograph method, was recalculated on the basis that oxygen contained atoms of masses 16, 17 and 18.[1] Later, liquid hydrogen was fractionated and examined for the atomic spectrum of hydrogen of mass 2. Clear evidence of the presence of heavy hydrogen was obtained.[2] This was followed by the discovery that in the electrolysis of water ordinary hydrogen is liberated more readily than heavy hydrogen. Consequently the systematic fractionation of water by electrolysis gives a residue rich in "heavy water." Under suitable conditions of electrolysis practically pure deuterium oxide ("heavy water") can be obtained.[3] In addition to the fractional distillation of hydrogen and the electrolysis of water, deuterium has also been isolated from hydrogen by diffusion and adsorption methods, from water by adsorption on charcoal and from water and acids by decomposition.[4]

The electrolysis of water is the most convenient method of obtaining deuterium. With relatively large supplies of deuterium available the physical properties of the element, the oxide ("heavy water") and other compounds such as deuterochloric acid (DCl) and deuteroammonia (ND_3) were recorded. This work was quickly followed by the examination of deutero-organic

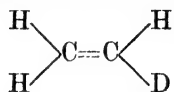
[1] Birge and Menzel, *Phys. Rev.*, 1931, **37**, 1670.

[2] Urey, Brickwedde, and Murphy, *Phys. Rev.*, 1932, **39**, 164 ; **40**, 1.

[3] Washburn and Urey, *Proc. Nat. Acad. Sci.*, 1932, **18**, 496 ; Lewis and Macdonald, *J. Chem. Phy.*, 1933, **1**, 341.

[4] Lewis, *J. Amer. Chem. Soc.*, 1933, **55**, 1297 ; Collie, *Nature*, 1933, **132**, 568 ; Taylor, Gould, and Bleakney, *Phys. Rev.*, 1933, **43**, 496 ; Lewis and Cornish, *J. Amer. Chem. Soc.*, 1933, **55**, 2616 ; Washburn and Smith, *J. Chem. Phys.*, 1933, **1**, 426 ; Bleakney and Gould, *Phys. Rev.*, 1933, **44**, 265 ; Horiuti and Polanyi, *Nature*, 1933, **132**, 819 ; A. and L. Farkas, *Nature*, 1933, **132**, 892.

compounds. These substances have been prepared either by the addition of deuterium or simple deuterium compounds to unsaturated compounds, or by the replacement of other atoms or groups by deuterium in saturated and unsaturated substances. The replacement of hydrogen by deuterium is of particular interest. Thus when ethylene is reduced by a mixture of hydrogen and deuterium some monodeuteroethylene,

$$\begin{matrix} H \\ H \end{matrix} \!\!> C{=}C <\!\! \begin{matrix} H \\ D \end{matrix}$$

is formed.

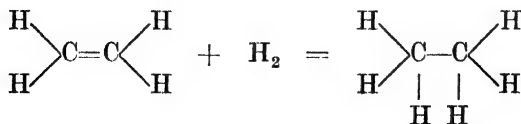
The discovery and isolation of deuterium places still another means of investigation at the disposal of chemists and a beginning has been made on molecular structural problems and on the mechanisms of reactions. Biologists have not been slow to make use of the new isotope, many interesting experiments have been performed and valuable information obtained by following the course of the element in biological changes. Some of the investigations are described below.

2. *Monodeutero-ethylene*

In the reduction of ethylene by a mixture of hydrogen and deuterium it was discovered that, in the presence of nickel as a catalyst under certain conditions, two reactions take place. The first change involves the replacement of hydrogen by deuterium in accordance with the following scheme :

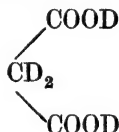
$$\begin{matrix} H \\ H \end{matrix} \!\!> C{=}C <\!\! \begin{matrix} H \\ H \end{matrix} \quad + \quad HD \quad \rightleftarrows \quad \begin{matrix} H \\ H \end{matrix} \!\!> C{=}C <\!\! \begin{matrix} H \\ D \end{matrix} \quad + \quad H_2$$

At the same time ordinary reduction took place :

$$\begin{matrix} H \\ H \end{matrix} \!\!> C{=}C <\!\! \begin{matrix} H \\ H \end{matrix} \quad + \quad H_2 \quad = \quad \begin{matrix} H \\ H \end{matrix} \!\!> \underset{H}{\underset{|}{C}}{-}\underset{H}{\underset{|}{C}} <\!\! \begin{matrix} H \\ H \end{matrix}$$

At 120° C. the replacement reaction was the faster. On the other hand, at 20° C. the major product was ethane. The course of these reactions was followed by measuring the gas pressure at

intervals, and at the same time determining the deuterium content of the hydrogen.[1]

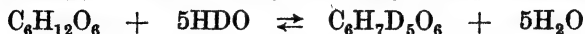
3. *Dideuteromalonic Deuteracid and Trideuteracetic Deuteracid*

The preparation of the acid, in which deuterium atoms take the place of all the hydrogen atoms of malonic acid may be described as an example of the interaction of a hydrogen-free substance and deuterium oxide. Carbon suboxide, which was conveniently prepared by decomposing diacetyltartaric anhydride at 625–650° C., was dissolved in benzene and mixed with deuterium oxide. After several days the reaction was complete and crystalline dideuteromalonic deuteracid

was isolated.

Trideuteracetic deuteracid ($CD_3 . COOD$) was obtained by decomposing the malonic acid at 140–150° C. under reduced pressure.[2]

4. *Carbohydrates*

When sucrose or glucose was dissolved in deuterium-rich water approximately half the hydrogen atoms of the sugar were exchanged with deuterium.[3] This interesting observation led to a fuller investigation of the exchange reactions in the carbohydrate group of compounds and it was found that hydroxyl hydrogen only was replaced. The free hexoses, *d*-glucose, *d*-mannose, *d*-galactose, *d*-fructose and their methyl glycosides, α-methylglucoside, α-methylmannoside and α-methylgalactoside, as well as 2 : 3 : 4 : 6-tetramethylglucose and mannitol were examined in water containing amounts of deuterium oxide varying from 11 to 96 per cent. The exchange reaction for an aldohexopyranose such as glucose may be represented as :

$$C_6H_{12}O_6 + 5HDO \rightleftarrows C_6H_7D_5O_6 + 5H_2O$$

[1] A. and L. Farkas and Rideal, *Proc. Roy. Soc.*, 1934, [A], **146**, 630; Tucholski and Rideal, *J.*, 1935, 1701.

[2] Wilson, *J.*, 1935, 492.

[3] Bonhoeffer and Brown, *Z. physik Chem.*, 1933, **1323**, 172; Moelwyn-Hughes, Klar and Bonhoeffer, *ibid.*, 1934, A, **169**, 114.

A quantity of the sugar under examination was dissolved in a known weight of heavy water and the solution allowed to stand to attain equilibrium. The solution was then vacuum distilled at room temperature, and a portion of the water forced into a pyknometer and weighed. The weight of the water before exchange was known. By assuming that each exchangeable hydrogen atom in the molecule had the same isotopic exchange equilibrium constant and by making certain other approximations, a simplified equilibrium equation was formulated which permitted the equilibrium constants for the exchanges to be calculated. Proceeding from this the number of exchangeable hydrogen atoms was calculated and found to be equal to the number of hydroxyl groups in the sugar molecule under examination.[1] These experiments demonstrated that it is only the hydrogen atoms of the hydroxyl groups that exchange with deuterium, and the good agreement between " exchange numbers " and hydroxyl groups in sugars and their derivatives opens up the possibility of a reasonably simple quantitative procedure for the determination of the hydroxyl group. This exchange behaviour is not confined to the hydroxyl groups of aliphatic compounds. Phenolic hydroxyl groups behave in a similar way, and the hydrogen atoms of amino and aldehydic groups also react rapidly.

5. *Phenols*

Phenol itself rapidly exchanges one of its hydrogen atoms when in contact with deuterium oxide in neutral solution, and in alkaline solution three more hydrogen atoms, presumably those in the *ortho*- and *para*-positions, become exchangeable.[2]

Resorcinol takes up two deuterium atoms very rapidly from deuterium oxide, and two further hydrogen atoms are exchanged at a measurable rate. It is considered that the two latter hydrogen atoms are from positions *ortho* to the hydroxyl groups and exchange by way of a keto-enol transformation. The two remaining nuclear hydrogen atoms of resorcinol are replaced very slowly. Quinol also has two hydrogen atoms which are very rapidly replaced by deuterium, but all four nuclear hydrogen

[1] Hamill and Freudenberg, *J. Amer. Chem. Soc.*, 1935, **37**, 1427.
[2] Ingold, Raisin and Wilson, *J.*, 1936, 1637.

atoms exchange very slowly and at the same rate. Apparently in this case there is no effective keto-enol change.[1] Pyrogallol exchanges three of its hydrogen atoms very rapidly when in contact with deuterium oxide, and the three remaining hydrogens are replaced more slowly, each at a different rate. On the other hand phloroglucinol has all its hydrogen atoms rapidly replaced by deuterium.

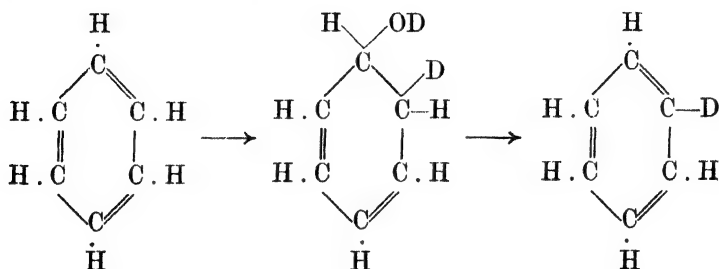
6. *Benzene*

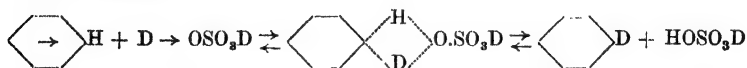
Deuterium has been introduced into the benzene nucleus in a variety of ways. Thus benzene when heated under pressure with water containing 3 per cent. of deuterium oxide in the presence of nickel as a catalyst, yielded some slightly deuterated benzene.[2] This method has been developed so that benzene containing practically only carbon and deuterium (C_6D_6), hexadeuterobenzene, can be prepared. The evacuated apparatus into which liquid benzene and deuterium oxide are introduced, was heated and the mixed vapours driven over the reduced nickel at 200° C. Frequent repetition of the process brought about an equilibrium partition of the deuterium between the water and benzene. The hydrogen diluted deuterium oxide was next replaced by fresh pure deuterium oxide and the process of passing the vapours over the catalyst continued until a highly deuterated benzene, containing over 99 per cent. of the hydrogen as deuterium, was obtained.[3]

A very pure hexadeuterobenzene has been prepared by hydrogen exchange between benzene and heavy sulphuric acid (D_2SO_4) without the aid of a heterogeneous catalyst. The heavy sulphuric acid was prepared from pure sulphur trioxide and deuterium oxide and the strength of the acid adjusted to 51 per cent. to avoid sulphonation of the benzene. The pure dry benzene was added to the acid and the mixture shaken at room temperature for 3–4 days, when equilibrium was reached. The partly deuterated benzene was separated from the reaction mixture and added to a fresh lot of heavy acid and the shaking continued. Four repetitions of this process and a final purification with barium oxide and phosphorus pentoxide yielded a

[1] Münzberg, *Z. physikal Chem.*, 1937, B **33**, 23, 39.
[2] Horiuti and Polanyi, *Nature*, 1934, **34**, 377.
[3] Bowman, Benedict, and Taylor, *J. Amer. Chem. Soc.*, 1935, **57**, 960.

benzene which analysis and density determination showed to contain at least 99·8 atoms per cent. of deuterium.[1] Two mechanisms have been suggested for the replacement of hydrogen by deuterium in benzene. On the one hand it is assumed that the elements of deuterium oxide first add on at a benzenoid double bond, and that this compound is then readily dehydrated by the acid to give deuterated benzene.[2] These ideas may be summarized as follows:

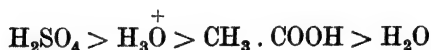
```
       H                H   OD                 H
       C               C    D                  C
H.C        C.H    H.C        C—H       H.C        C—D
 ||         |  →   ||         |    →    ||         |
H.C        C.H    H.C        C.H       H.C        C.H
       C                C                  C
       H                H                  H
```

On the other hand, this ethylenic type of addition and elimination is not regarded as plausible when applied to aromatic compounds. The exchange is regarded as an electrophilic substitution by attack at a single carbon atom, with the polarizability of the benzene system available to assist the formation of an additional partial bond. Representing the polarizations of benzene and heavy sulphuric acid as ⟨→⟩ H and D → $O.SO_3D$ respectively, the exchange may be represented graphically in the following way:

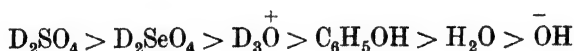
$$\langle\rightarrow\rangle H + D \rightarrow OSO_3D \rightleftarrows \langle\;\rangle\!\!<^{H}_{D} O.SO_3D \rightleftarrows \langle\;\rangle D + HOSO_3D$$

The sulphonation and subsequent desulphonation of the benzene sulphonic acid formed need not be considered as this acid has been shown to resist desulphonation under the conditions of the exchange.[3]

The electrophilic substitution theory of the exchange mechanism is supported by the fact that deuteration of benzene derivatives by acidic reagents follows the known rules for orientation

[1] Ingold, Raisin and Wilson, *Nature*, 1934, **134**, 734; *J.*, 1936, 715.
[2] Horiuti and Polanyi, *Nature*, 1934, **134**, 847.
[3] Ingold, Raisin, and Wilson, *J.*, 1936, 715.

and velocity in electrophilic aromatic substitutions. For example the substituents $—SO_3H$, $—NO_2$, —Cl, and —Br in the benzene nucleus should retard deuteration. On the other hand, the presence of $—CH_3$, —OH, $—O.CH_3$ and $—N\langle{}^{CH_3}_{CH_3}$ should accelerate the entry of deuterium into the nucleus. The experimental results for the rate of deuteration of benzenesulphonic acid, benzene, anisole, dimethylaniline and phenol fit in with the theoretical requirements. Similarly this mechanism theoretically requires that the deuterating power of different acid reagents should be parallel with the hydrion-donating power of the same reagents containing hydrogen. For instance the series

$$H_2SO_4 > H_3\overset{+}{O} > CH_3.COOH > H_2O$$

represents hydrion-donating power. Experimentally the deuterating efficiencies of the reagents examined fell into the following order

$$D_2SO_4 > D_2SeO_4 > D_3\overset{+}{O} > C_6H_5OH > H_2O > \overset{-}{O}H$$

in agreement with the conception of deuteration as an electrophilic aromatic substitution of the ordinary type.[1]

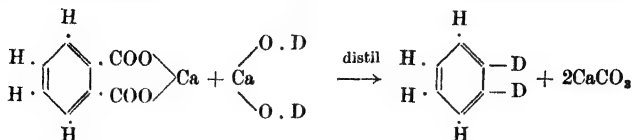
The replacement of hydrogen by deuterium in benzene leaves the nuclear charges unaltered and consequently the whole effect on the vibration frequencies may be regarded as due to the known changes in the atomic masses, and on this basis a comparative study of the long-wave spectroscopy of benzene and hexa-deuterobenzene was made to throw light on the fine structure of benzene. This comprehensive survey included the examination of the Raman, infra-red, fluorescence and resonance spectra of benzene and hexa-deuterobenzene. An analysis of the spectroscopic results showed that the structural requirements were more nearly fulfilled by a plane regular hexagonal model than by the Kekulé or trigonally puckered models.[2]

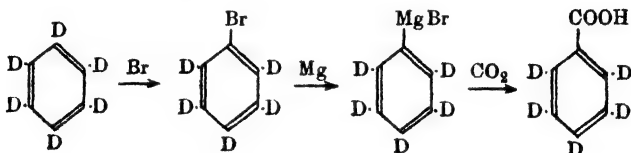
Partly deuterated benzenes of known orientation may be prepared by distillation of the calcium salts of benzene carboxylic

[1] Ingold, Raisin, and Wilson, *J.*, 1936, 1637.

[2] Ingold et al., *Nature*, 1934, **134**, 734, 847; *J.*, 1936, 912–987; Wilson, *J.*, 1936, 1210.

acids with calcium deuteroxide.[1] The following scheme illustrates this method for the preparation of *o*-dideuterobenzene.

$$C_6H_4\begin{matrix}COO\\COO\end{matrix}\!\!>Ca + Ca\begin{matrix}O.D\\O.D\end{matrix} \xrightarrow{\text{distil}} C_6H_4\begin{matrix}-D\\-D\end{matrix} + 2CaCO_3$$

Many other derivatives of benzene have been prepared. For example, pentadeuterobenzoic acid has been obtained from hexadeuterobenzene by the following steps :

$$C_6D_6 \xrightarrow{Br} C_6D_5Br \xrightarrow{Mg} C_6D_5MgBr \xrightarrow{CO_2} C_6D_5COOH$$

7. *Biological Applications*

In physiological work it is extremely difficult to follow the course of administered substances in the animal body. Certain easily detectable groups such as halogens or phenyl radicles may be introduced into the molecule, but such compounds differ so greatly in chemical and physical properties from the natural fat, amino-acid or other substance to be administered that they are dealt with differently by the body. Consequently problems of normal transport and metabolism cannot be studied by means of such materials. If, however, an element can be introduced into a physiological compound, which affects its chemical and physical properties to so small an extent that the animal organism cannot differentiate between the normal and " labelled " substance, the interpretation of the results obtained would be simplified. It is, of course, necessary that the detection and estimation of the " labelling " element should be possible by chemical or physical means. A small number of isotopes both stable and radio-active have been employed in biological work. The determination of stable isotopes such as those of carbon or nitrogen, however, involves either oxidation of carbon to carbon dioxide or the reduction of nitrogen to the elementary state before the isotope ratio can be determined by means of the mass spectograph.

[1] Morita and Titani, *Bull. Chem. Soc. Japan*, 1935, **10**, 557 ; Redlich and Stricks, *Monatsh.*, 1936, **68**, 47, 374 ; Weldon and Wilson, *Nature*, 1936, **137**, 70.

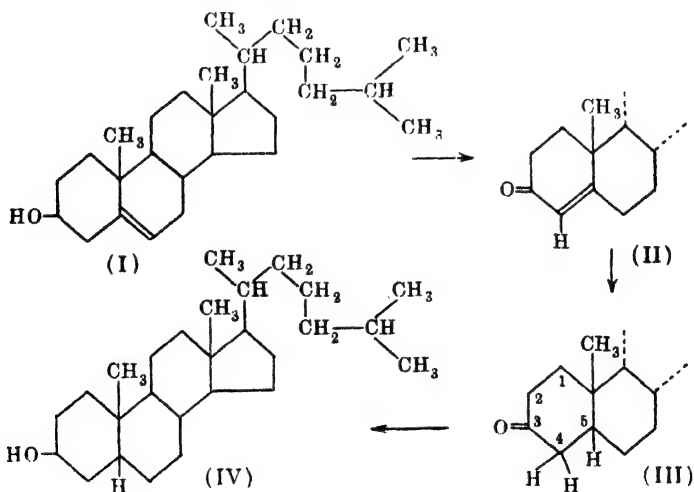
The use of radioactive isotopes in biological work has many advantages, and these are conveniently detected by means of a beta-ray Geiger counter. A serious drawback is the very short-half-life of some of the important elements; for nitrogen it is 9·9 seconds and for lithium 0·88 seconds. The use of deuterium as an indicator in biological work has the advantages that the hydrogen and deuterium in combination in an organic compound can be converted into "water." This can be readily purified and the density difference between normal water and water containing deuterium rapidly and accurately determined. Deuterium has been used as an indicator in biological work in two principal ways. In the first method deuterium is introduced into an organic compound by synthesis, and this substance fed or injected into a living organism. If the synthetic compound is broken down during metabolism the deuterium is liberated as "heavy water" and can be recovered from the blood or urine. If the compound is deposited or converted without the deuterium bond being affected, the deuterium can be recovered as "heavy water" from the organs by combustion.

In the second method a suitable amount of deuterium oxide may be injected into the living animal and the established concentration maintained by further additions in the drinking water. During the period when a definite concentration of deuterium is maintained in the animal body any organic compound formed there by synthesis will contain some deuterium. From the substances isolated and examined information may be obtained regarding the synthetic processes in the living organism. In illustration of the former method two investigations may be described; the first on the metabolism of fat and the second on the changes undergone by cholesterol in the animal body.

Mice were fed for several days on a diet comprising a partially deuterised linseed oil. This oil was considered to be equivalent to a natural fat, and was prepared by the catalytic reduction of linseed oil with deuterium. The animals were kept on a diet, which was insufficient in quantity for them to maintain their weight. In spite of the fact that the animals had lost weight, it was found that a large proportion of the absorbed deuterated material was deposited in the fat depots,* clearly indicating that

* The fat depots are the abdominal cavity and the region under the skin.

the fat which was burned was not oxidised directly after absorption, but had been taken from the fat depots. In one set of experiments 47 per cent of the ingested fat was found in the depots and "heavy water" equivalent to 20 per cent. of the ingested fat in the body fluids. A small amount of the absorbed fat was found in the internal organs. The unexpected result of these experiments was that the largest part of the diet fat was deposited in the fat tissues before it was utilized.[1]

Turning now to the second investigation, coprosterol (IV) is formed in large amounts from cholesterol (I) in the animal body. Many attempts have been made to throw light on the mechanism of the change. *In vitro* cholesterol can be converted into coprosterol via cholestenone (II) and coprostanone (III), and it was thought that *in vivo* the change followed the same course. The scheme of structures is given below :—

If the animal body forms coprosterol in this way, both cholestenone and coprostanone should give rise to coprosterol when fed to animals. It is known that dogs fed on a meat diet excrete coprosterol, and on many other diets eliminate cholesterol. In the investigation under review a dog was first fed on dog biscuits with the result that cholesterol was excreted. When cholestenone was added to this diet there was an appreciable increase

[1] Schoenheimer et al., *J. Biol. Chem.*, 1935, **111**, 163–192.

in the amount of cholesterol eliminated. The same animal on a meat diet excreted coprosterol, and the addition of cholestenone to the food induced an excess of coprosterol excretion. In order to make sure that the coprosterol was actually formed from cholestenone, the latter was catalytically reduced by deuterium to coprostanone with deuterium atoms at the positions 4 and 5 in the molecule. (See structure III.)

This "heavy" ketone was added to the meat diet of a dog daily for four days. The excreted sterols were subjected to combustion and the deuterium oxide content of the water formed estimated. From the results obtained it was concluded that between 10 and 20 per cent. of the coprosterol in the faeces was derived from the ingested "heavy" coprostanone, and that in the body the formation of coprosterol from cholesterol follows the course outlined above.

This section may be concluded with a brief account of the method of studying vital syntheses in a medium of heavy water.

When the drinking water of an animal was replaced by a dilute solution of heavy water, the concentration of deuterium oxide in all the body fluids became approximately constant after a short time. In the mice used experimentally the concentration of deuterium in the body fluids was maintained at 1·5 per cent. Analyses of the body fluids and the organic materials showed that the amount of deuterium in the fatty acids had reached a maximum after six to eight days. As the concentration of deuterium in the body fluids was also constant, a state of equilibrium between fatty acids and body fluids must have been established in this time. The deuterium found in the fatty acids is the uptake of non-exchangeable deuterium and represents a synthesis of fatty acids. After six to eight days nearly all the original fatty acids had been replaced by newly formed ones, and therefore a continuous and rapid turnover of the fatty acids had taken place in the living organism. In these experiments the mice received a carbohydrate-rich and fat-poor diet; and from the results obtained it seems probable that new fatty acids were synthesized continuously from the carbohydrates of the diet.[1]

[1] Schoenheimer and Rittenberger, *J. Biol. Chem.*, 1936, **114**, 381; 1937, **121**, 235.

CHAPTER X

SOME CASES OF ISOMERISM IN CYCLIC COMPOUNDS

1. *The Space Models of Hexamethylene*

When a six-membered ring is built up from the tetrahedal models used for stereochemical demonstration, it is found that, without undue strain, it is impossible to force all the six atoms into one plane. As Sachse [1] pointed out, two strainless arrangements are possible, photographs of which are given in Plate I.

Examination of these illustrations will show that a plane drawn through the atoms, 2, 3, 5, 6, will not contain the atoms 1 and 4 in either model. Further, in Type A, the atoms 1 and 4 lie on the same side of the plane containing 2, 3, 5, 6 ; whilst in Type B, the atoms 1 and 4 lie on opposite sides of this plane.

If the structures were perfectly rigid, a number of results would follow :—

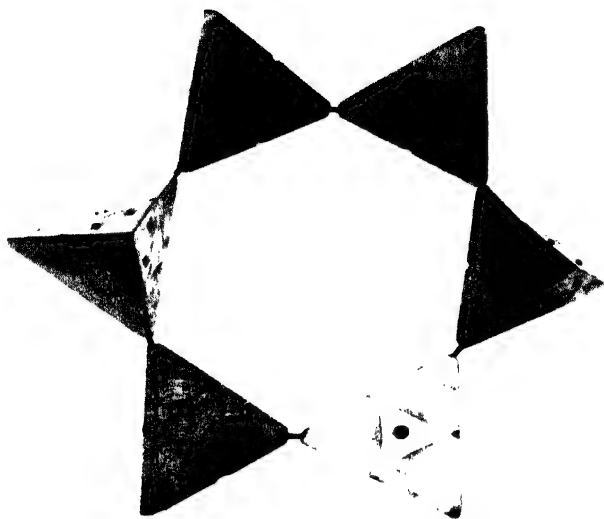
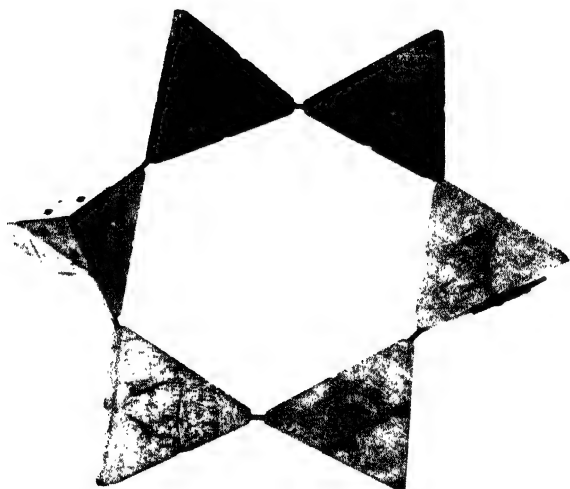
(1) There should be two isomeric hexamethylenes, one corresponding to Type A, the other having the configuration of Type B.

(2) Every mono - substitution - product of hexamethylene should occur in two forms, since in either of the models there are two distinct sets of hydrogen atoms : the group 2, 3, 5, 6, in one plane, and the pair 1, 4, which are not in this plane.

(3) *Cis*-hexahydrophthalic acid should be capable of resolution into optical antipodes if the configuration of any of its molecules is of the Type B.

In practice, hexamethylene itself and all its mono-substitution-products are found to be homogeneous ; and the attempt to resolve *cis*-hexahydrophthalic acid into its antipodes proved a failure.[2] These facts suggest that neither Type A nor Type B can represent hexamethylene correctly.

[1] Sachse, *Ber.*, 1890, **23**, 1363 ; *Z. physikal. Chem.*, 1892, **10**, 203.

[2] Werner and Conrad, *Ber.*, 1899, **32**, 3046.

TYPE A.

TYPE B.

THE TWO SPACE-MODELS OF HEXAMETHYLENE

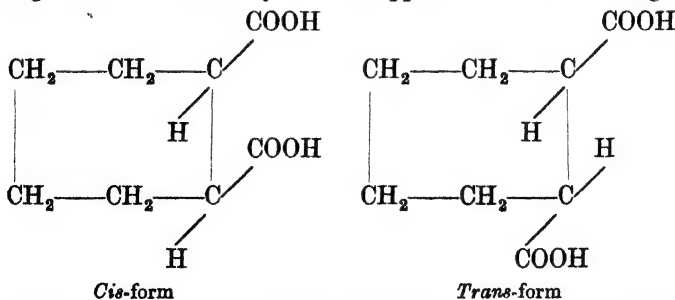
A possible explanation of the state of affairs is found when slight pressure is applied to the atom 1 in either model. It is then found that very little effort forces the model from the Type A configuration into the Type B form, and *vice versa.* If the same holds good in the molecule itself, then it is easy to see that a labile system of this sort would evade the difficulties set forth above.

This however, would not apply to the solid state; and from an X-ray examination of the crystal-structure of benzene hexahalides, $C_6H_6X_6$, Hendricks and Bilicke [1] arrived at the conclusion that so far as hexamethylene goes, the spatial arrangement of the atoms in hexamethylene is more complex than is suggested by the simple tetrahedral models.

2. *Mohr's Views on Fused Rings*

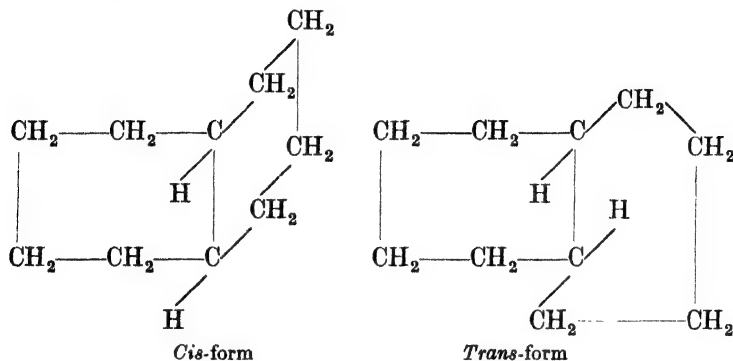
It was pointed out by Mohr [2] that although the simple hexamethylene ring can escape the production of isomerism by a simple distortion, the conditions are altered when a second ring is fused on to the primary one in such a manner that two adjacent atoms are common to both cyclic systems. In this case, the model can still undergo distortion; but more force is required to change the one configuration into the other; and in one special type, an isomerism is possible which cannot be eliminated by any simple twisting.

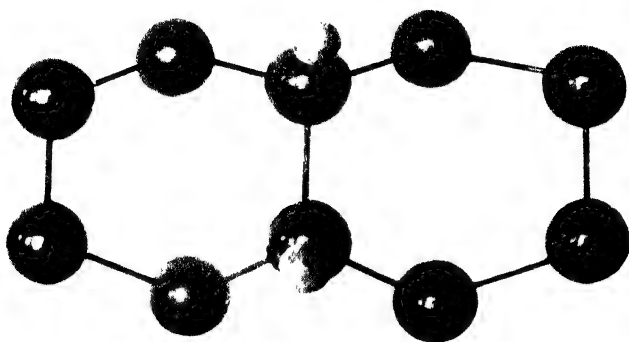
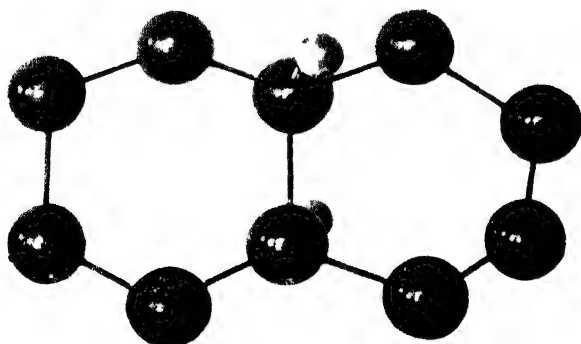
A preliminary consideration of the isomeric hexahydrophthalic acids will make the matter quite simple. These acids occur in two stereoisomeric forms, in one of which the two carboxyl groups lie on the same side of the ring, whilst in the isomeric configuration, the carboxyls lie on opposite sides of the ring:—

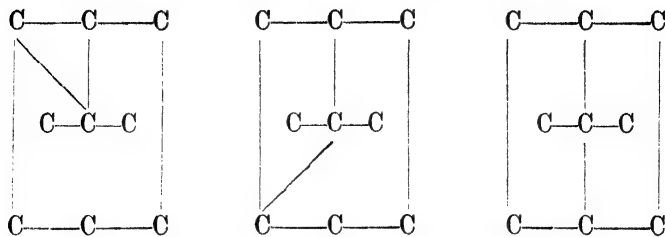
Cis-form   *Trans*-form

[1] Hendricks and Bilicke, *J. Amer. Chem. Soc.*, 1926, **48**, 3007.
[2] Mohr, *J. pr. Chem.*, 1928, **98**, 315.

Inspection will show that no twisting of the molecule will suffice to convert the one variety into the other, so long as the bonds remain intact.

Now imagine that in each model the carboxyl groups are removed and that, in their places, the two ends of a —CH_2 . CH_2 . CH_2 . CH_2— chain are inserted, yielding decalins, $C_{10}H_{18}$. The *cis-trans* peculiarities will remain; and the result will be two models which can be represented by the following formulae :—

Cis-form *Trans*-form

Photographs of these two structures are shown in Plate II. The hydrogen atoms of the methylene groups have been omitted from the model for the sake of clarity. From an inspection of the illustration it will be clear that no twisting of the model can alter the relative positions of the two rings, since these depend upon the points of attachment of the cyclic groupings to the two central carbon atoms of the system: an arrangement which could be altered only by actual rupture of the bonds concerned.

On building up the model, it is found that the system is practically strainless, owing to the manner in which the atoms arrange themselves in three dimensions. (See Plate II.) Mohr regards it as strange that rings of this description do not occur among the natural products, since bicyclic systems of this kind could evidently be formed from open chains with very little expenditure of energy. Yet among the naturally-occurring cyclic substances the tendency is to form rings of types whic entail far greater strains, such as :—

Cis-form.

Trans-form.

SPACE-MODELS SHOWING THE ISOMERISM IN REDUCED NAPHTHALENE RINGS.

This is, however, hardly a fair presentation of the facts. All the evidence suggests that the terpenes, for example, are built up by the combination of isoprene molecules or analogous units; and in the passage from an open chain to a cyclic structure it is clear that two influences may be working against each other: the effort to form a stable, saturated arrangement, on the one hand, and the difficulty involved in overcoming the strain of ring-closure on the other. The result produced will be due to a balancing of these factors and can hardly be paralleled by the direct formation of saturated rings, as Mohr's statement seems to imply.

A more interesting problem arises when the space formulae of the decalins are examined. Two forms are obviously capable of existence in the model: the *cis*-form and the *trans*-form. The model suggested that these isomeric forms should be quite stable; and Mohr's ideas opened the way into a fresh field of research.

3. *The Decalins and their Analogues*

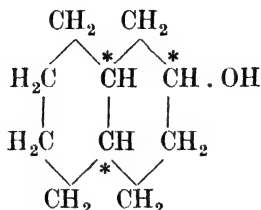
The early history of the reduced naphthalene derivatives becomes quite clear in the light of Mohr's suggestions; but while the investigation of these compounds was actually in progress, a considerable amount of misunderstanding occurred, owing to the lack of the true key to the problem.

In 1905, Leroux[1] obtained a decahydro-β-naphthol, $C_{10}H_{17}.OH$, by repeated hydrogenation of β-naphthol below 200° C. This material melted at 75° C. Two years later, Ipatieff[2] prepared a decahydro-β-naphthol which apparently had the melting-point 99°–100° C. When a specimen of Ipatieff's compound was examined by Mascarelli and Recusani,[3] it was found to be a mixture of two isomerides, melting at 75° and 105° C.

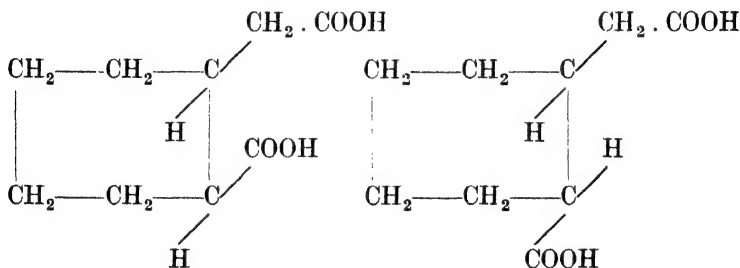
Now the complete hydrogenation of β-naphthol results

[1] Leroux, *Compt rend.*, 1905, **140**, 590. [2] Ipatieff, *Ber.*, 1907, **40**, 1281.
[3] Mascarelli and Recusani, *Gazzetta*, 1912, **42**, II, 35.

in the production of asymmetric carbon atoms marked with asterisks in the formula :

```
      CH2   CH2
     /   \*/   \*
 H2C      CH    CH.OH
  |       |     |
 H2C      CH    CH2
     \   /*\   /
      CH2   CH2
```

and Mascarelli and Recusani naturally adopted the obvious explanation and accounted for the isomerism by postulating the existence of several racemic compounds, two of which were assumed to correspond to the components in Ipatieff's mixture.

Fresh facts came to light in the course of an investigation of the anhydride-formation of dicarboxylic acids.[1] When homophthalic acid (*o*-carboxy-phenylacetic acid) is hydrogenated in glacial acetic acid solution in presence of platinum black, it yields a mixture of the *cis*- and *trans*-forms of *o*-carboxy-cyclohexane-acetic acid :—

```
                    CH2.COOH                           CH2.COOH
                   /                                  /
CH2----CH2----C/                   CH2----CH2----C/
 |            /|                    |            /|
 |           H |  COOH              |           H |   H
 |             |  /                 |             |  /
CH2----CH2----C/                   CH2----CH2----C/
             /                                  /
            H                                 COOH
```

As was anticipated, the *cis*-acid was transformed into the corresponding *cis*-anhydride by heating it with acetic anhydride, M.P. 57° C. But from the *trans*-acid, a second anhydride was obtained, with the M.P. 80°–81° C. When either isomer is heated to 220° C. for a time, an equilibrium mixture is obtained which contains 25 per cent. of the *cis*-anhydride and 75 per cent. of the *trans*-anhydride.

By this time, Mohr's views had been published ; and the two anhydrides were recognised as *cis-trans* isomerides in accordance with his theory, since the anhydride bridge forms the necessary second ring in the molecular structure.

[1] Windaus, Hückel, and Reverey, *Ber.*, 1923, **56**, [*B*], 91.

Attention now reverted to the reduction-products of β-naphthol.[1] On oxidizing these isomeric decahydro-β-naphthols, it was found that two isomeric ketones were obtained. This disproved the original assumption that the isomerism had its origin in the asymmetry of the groups —CH . OH— since this asymmetry is destroyed by the conversion of the secondary alcohol radicle into the carbonyl group. On Mohr's theory, the isomerism of the ketones is simply accounted for by assuming the existence of *cis*- and *trans*-forms; and the production, on further oxidation, of the corresponding pair of isomeric acids is also easily explicable :—

Cis-forms

CH . OH
CH_2
CH_2—CH_2—C CH_2
H CH_2
CH_2—CH_2—C
H

↓ oxidation

CO
CH_2
CH_2—CH_2—C CH_2
H CH_2
CH_2—CH_2—C
H

↓ oxidation

COOH
CH_2—CH_2—C
H $CH_2.CH_2$ COOH
CH_2—CH_2—C
H

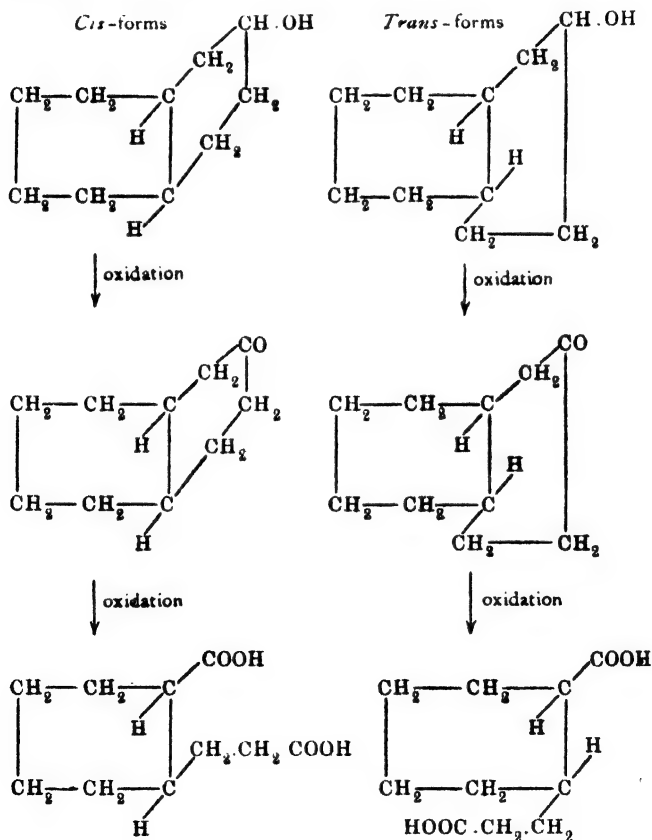
Trans-forms

CH . OH
CH_2
CH_2—CH_2—C
H
H
CH_2—CH_2—C
CH_2—CH_2

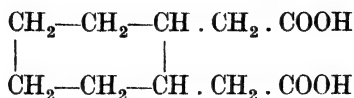
↓ oxidation

CO
CH_2
CH_2—CH_2—C
H
H
CH_2—CH_2—C
CH_2—CH_2

↓ oxidation

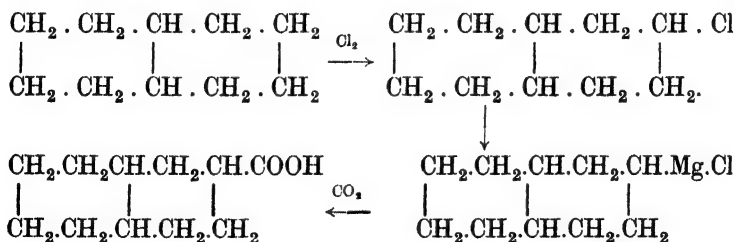
COOH
CH_2—CH_2—C
H
H
CH_2—CH_2—C
HOOC . CH_2 . CH_2

[1] Hückel, *Nach. K. Ges. Wiss. Göttingen*, 1923, 43.

The final oxidation to the acids produces also a second pair of isomers which are obviously *cis*- and *trans*-forms of the acid

$$\begin{array}{l} CH_2—CH_2—CH\,.\,CH_2\,.\,COOH \\ |\qquad\qquad\quad | \\ CH_2—CH_2—CH\,.\,CH_2\,.\,COOH \end{array}$$

The isomeric decahydronaphthalenes themselves have been obtained from the ketones formulated above by first forming the semicarbazone and acting on this with sodium and alcohol,[1] or by the catalytic reduction of naphthalene itself.[2] The *cis*-compound has a B.P. of 193°/768 mm., whilst the *trans*-compound boils at 185°/756 mm. It is curious to note that reduction with a platinum catalyst leads to the production of about 90 per cent. *cis*- and 10 per cent. *trans*-form, whilst when a nickel catalyst is employed the product is mainly the *trans*-isomer. From these results it is obvious that commercial decalin is a mixture of the two stereoisomers; and this has been definitely established [3] by chlorinating decalin and then treating a Grignard reagent prepared from the chlorinated product with carbon dixoide to form the corresponding carboxylic acids, which were then identified by comparison with the acids obtained by a similar process from each stereoisomer of decahydronaphthalene separately.

$$\begin{array}{l} CH_2\,.\,CH_2\,.\,CH\,.\,CH_2\,.\,CH_2 \\ |\qquad\qquad |\qquad\qquad | \\ CH_2\,.\,CH_2\,.\,CH\,.\,CH_2\,.\,CH_2 \end{array} \xrightarrow{Cl_2} \begin{array}{l} CH_2\,.\,CH_2\,.\,CH\,.\,CH_2\,.\,CH\,.\,Cl \\ |\qquad\qquad |\qquad\qquad | \\ CH_2\,.\,CH_2\,.\,CH\,.\,CH_2\,.\,CH_2. \end{array}$$

$$\downarrow$$

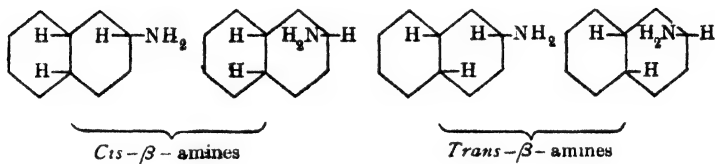
$$\begin{array}{l} CH_2.CH_2CH.CH_2.CH.COOH \\ |\qquad\quad |\qquad\quad | \\ CH_2.CH_2.CH.CH_2.CH_2 \end{array} \xleftarrow{CO_2} \begin{array}{l} CH_2.CH_2.CH.CH_2.CH.Mg.Cl \\ |\qquad\quad |\qquad\quad | \\ CH_2.CH_2.CH.CH_2.CH_2 \end{array}$$

Among the substitution-products of the decanaphthalenes which have been studied up to the present, reference may be made to the decahydro-β-naphthoamides. Four of these are

[1] Eisenlohr and Polenske, *Ber.*, 1924, **57**, [*B*], 1639.

[2] Willstätter and Seitz, *Ber.*, 1924, **57**, [*B*], 683; Hückel, *Annalen*, 1925, **441**, 1; *Ber.*, 1925, **58**, [*B*], 1449; Hückel and others, *Annalen*, 1926, **451**, 109.

[3] Borsche and Lange, *Annalen*, 1923, **434**, 219.

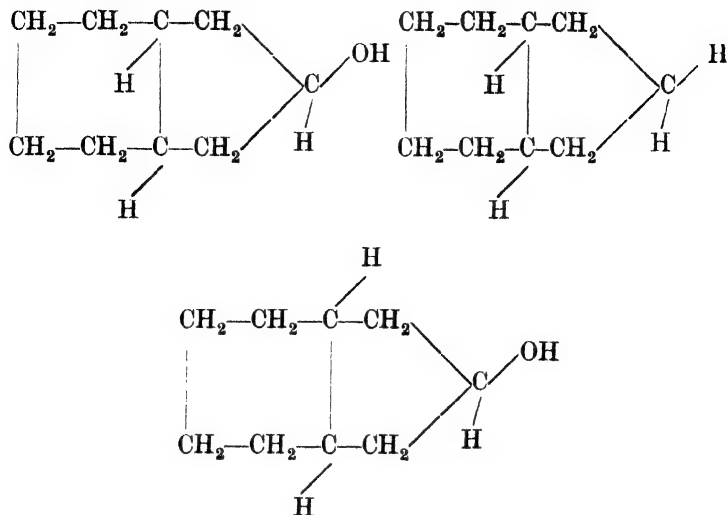
theoretically possible; and out of this number two have been isolated by Borsche and Lange,[1] and a third by Kay and Stuart.[2] In the case of β-hydroxy-(β-decalol) and β-amino-decahydro-naphthalenes (β-decalylamines), all four isomers have been obtained. The amines were prepared from the *cis*- and *trans*-β-decalone oximes by reduction. Hydrogenation of the *cis*-oxime yielded one *cis*-β-decalylamine, whilst the action of sodium and alcohol produced a mixture from which a second *cis*-β-decalyl-amine was isolated. In the same way *trans*-β-decalone oxime afforded two different *trans*-β-decalylamines.[3] The structures of the amines may be represented as follows :—

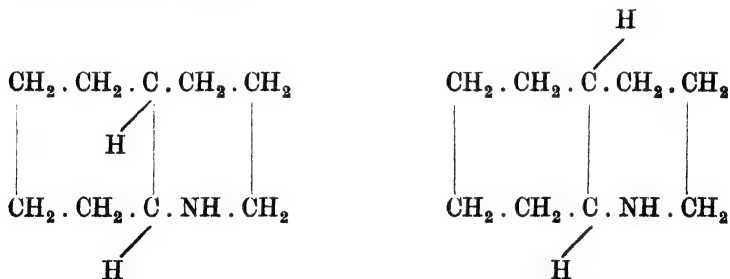
Cis-β-amines *Trans*-β-amines

The corresponding four α-substituted amines have also been prepared and examined, but these were more difficult to obtain owing to the ease with which *cis*-α-decalone isomerizes into the *trans*-compound.[4] In the case of the β-hydroxy- and β-aminodecahydronaphthalenes, all four isomers have been obtained.[5]

4. *Other Ring-Systems*

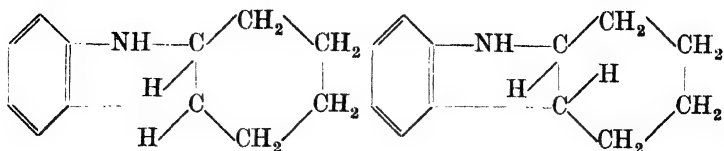
It is evident that this type of isomerism may show itself in other cases wherein two rings have a couple of atoms in common; and already several examples have been detected.

Three forms of hexahydro-β-hydrinol have been isolated,[6] two being *meso*-forms and the third a racemic variety.

[1] *Ibid.*, 1923, **434**, 219.
[2] Kay and Stuart, *J.*, 1926, 3038.
[3] Hückel et al., *Annalen*, 1926, **451**, 109; *Ber.*, 1934, **67**, [B], 1890.
[4] *Idem*, *Annalen*, 1933, **502**, 99.
[5] Hückel and others, *Annalen*, 1926, **451**, 109.
[6] Hückel and Friedrich, *Annalen*, 1926, **451**, 132.

By hydrogenating quinoline by means of platinum black in a solution of acetic acid containing hydrochloric acid, the product was found to contain 65 per cent. of a new isomeride of decahydroquinoline.[1] The two possible configurations obviously are those shown below :

```
                                                        H
                                                       /
CH2 . CH2 . C . CH2 . CH2          CH2 . CH2 . C . CH2 . CH2
|          /|          |           |           |          |
|         H |          |           |           |          |
|           |          |           |           |          |
CH2 . CH2 . C . NH . CH2           CH2 . CH2 . C . NH . CH2
           /                                  /
          H                                  H
```

An interesting case is provided by hexahydrocarbazole,[1] for here there are three ring-systems fused together. When tetrahydrocarbazole is reduced with tin and hydrochloric acid, a yield of 1 per cent. to 2 per cent. of a previously unknown hexahydro-derivative was isolated. The two isomerides may be formulated thus :—

[1] Hückel and Stepf, *Annalen*, 1927, **453**, 163.
[1] Gurney, Perkin, and Plant, *J.*, 1927, 2676.

```
              /CH2\                          /CH2\
  C6H4—NH—C/      \CH2     C6H4—NH—C/      \CH2
        H/ |         |           H/ |  /H     |
  ...      C        CH2     ...    --C/      CH2
        H/  \CH2/                    \CH2/
```

The foregoing facts seem ample to establish the correctness of Mohr's speculations.

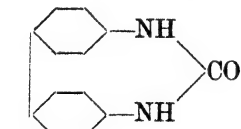
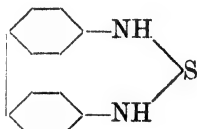
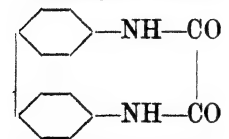
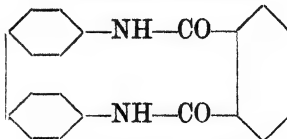
CHAPTER XI

THE DIPHENYL PROBLEM

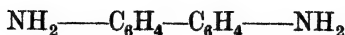
1. *The Kaufler Hypothesis*

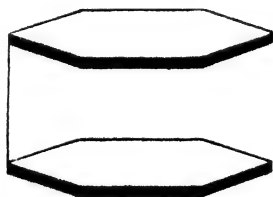
In science, even erroneous hypotheses may have their uses; and the history of the diphenyl isomerism furnishes one of the best examples of this fact. Here was a case in which a number of isolated data were brought together under a single head by means of a simple hypothesis; and then, when further work showed that the hypothesis was untenable, investigators were stimulated to check the original evidence in its favour; and finally, it was found that mistakes had been made in many cases. Without the incentive provided by the hypothesis, these erroneous statements would never have been checked as a whole; and the reference books might easily have misled later workers who had need of the particular compounds which were misdescribed.

It is an ungrateful task to chronicle honest errors; and the first stage in the history of the diphenyl problem need not be dealt with in any great detail. One or two examples will be quite sufficient.

By acting on benzidine with reagents such as carbonyl chloride, various compounds were obtained to which the following formulae were ascribed :—

I. Carbonyl-benzidine [1] II. Thiocarbo-benzidine [2]

III. Oxalyl-benzidine [3] IV. Phthalyl-benzidine [4]

[1] Michler and Zimmermann, *Ber.*, 1881, **14**, 2178.
[2] Borodine, *Jahresbericht*, 1860, 356.
[3] Schiff and Vanni, *Annalen*, 1890, **258**, 363. [4] Kolber, *Ber.*, 1904, **37**, 2882.

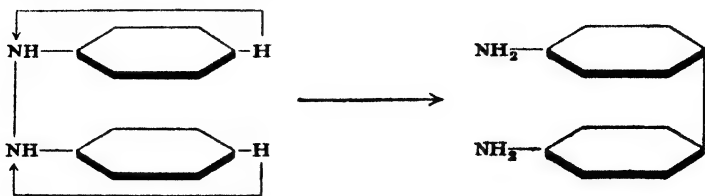
In each of these cases, it will be noticed, the reagent is assumed to have attacked the two amino-groups simultaneously. Now if the benzidine molecule be represented by :—

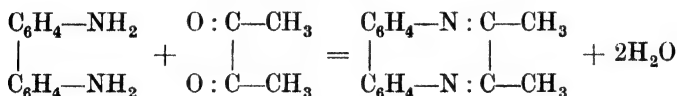
$$NH_2—C_6H_4—C_6H_4—NH_2$$

the amino-groups should be far apart in space and therefore unlikely to react simultaneously with, say, carbonyl chloride.

This peculiarity suggested to Kaufler [1] the idea that in the diphenyl molecule the two rings might lie in planes * in such a way that the positions *para* to the points of junction would be adjacent in space :—

In this diagram, the two rings are supposed to be lying in planes perpendicular to the plane of the paper ; and the heavily-printed lines indicate the sides of the hexagons which are nearest to the reader.

When Kaufler's views were put forward, Baeyer's Strain Theory was still supposed to represent facts fairly well ; for nothing higher than nonomethylene had been obtained among the simpler cyclic compounds, and it was supposed that there were great difficulties in the way of a synthesis of rings containing a large number of atoms. With these ideas in the air, it was natural that Kaufler's suggestion should receive a certain support, since it seemed to offer a means of accounting for the stable existence of the eleven- and fourteen-membered rings shown in the formulae above. Further, when applied to the benzidine change, it suggested a simple explanation of the mysterious *para*-coupling which is the marked feature of that rearrangement.

[1] Kaufler, *Annalen*, 1907, **351**, 151 ; *Ber.*, 1907, **40**, 3250.

* Kaufler's actual statement was that the planes of the rings were inclined at an angle to each other, but his diagrams showed them lying parallel.

For a time, the Kaufler hypothesis held the field ; and various pieces of research were fitted to it. Only one of these need be mentioned here. Since on Kaufler's assumptions the two amino-groups of benzidine are adjacent in space, it seemed possible that they could be made to react with the carbonyl groups of α-diketones so as to form cyclic compounds thus :—

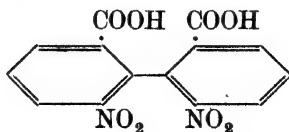
$$\begin{array}{l} C_6H_4\text{—}NH_2 \\ | \\ C_6H_4\text{—}NH_2 \end{array} + \begin{array}{l} O:C\text{—}CH_3 \\ \quad | \\ O:C\text{—}CH_3 \end{array} = \begin{array}{l} C_6H_4\text{—}N:C\text{—}CH_3 \\ | \qquad\qquad\ \ | \\ C_6H_4\text{—}N:C\text{—}CH_3 \end{array} + 2H_2O$$

Condensation of benzidine with diacetyl and with dibenzil was found to be practicable ; and it was assumed that the products were of the type shown above.

It was in connection with these compounds that the Kaufler hypothesis sustained an initial shock. Further investigation [1] established that their constitutions were not of the type which Kaufler's ideas suggested. But in the meanwhile light was thrown on the subject from a fresh direction by the study of the diphenic acids.

2. *Substitution-products of the Diphenic Acids*

By oxidizing the nitration-products of phenanthraquinone and also by direct nitration of diphenic acid, Schultz [2] obtained a dinitrodiphenic acid. As a result of an examination of this acid, Schmidt and Kämpf [3] came to the conclusion that it was 2 : 2′-dinitro-diphenic acid :—

COOH COOH

NO_2 NO_2

The synthesis of the acid had not been carried out, however, and as a rigid proof of its constitution was required in the course of

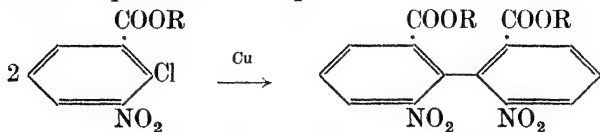
[1] Ferriss and Turner, *J.*, 1920, **117**, 1140. [2] Schultz, *Annalen*, 1880, **203**, 95.
[3] Schmidt and Kämpf, *Ber.*, 1903, **36**, 3745.

a research by Kenner and Stubbings, these workers [1] proposed to prepare it in the following manner.

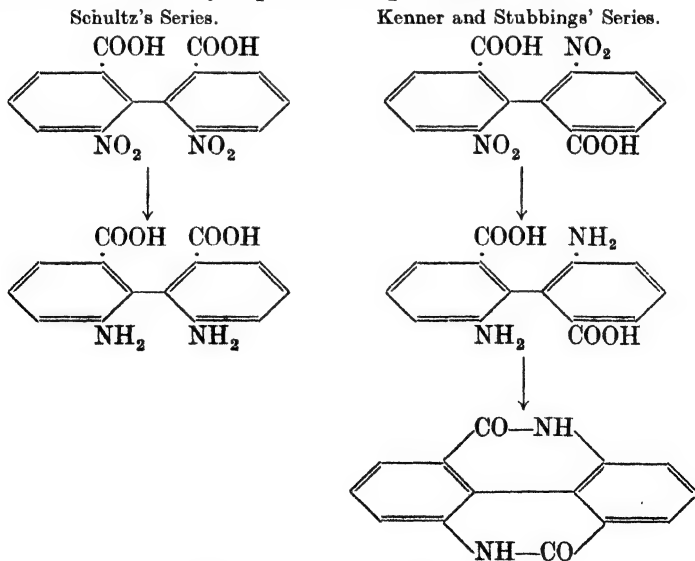
By oxidizing 2-chloro-3-nitrotoluene with dilute nitric acid, 2-chloro-3-nitrobenzoic acid was obtained; and on treating the ester of this last compound with copper powder, the ester of 6 : 6′-dinitro-diphenic acid was produced.

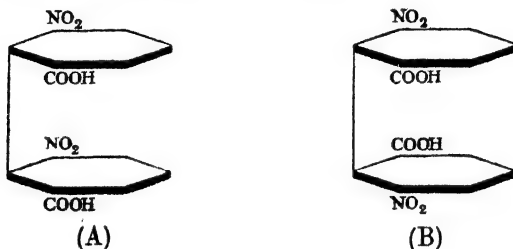
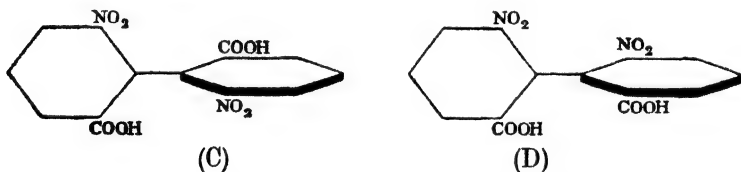
COOR　　　　　　COOR　COOR

2 ⟨ ⟩Cl $\xrightarrow{\text{Cu}}$ ⟨ ⟩—⟨ ⟩

NO_2　　　　　　NO_2　NO_2

On hydrolysis, this ester yielded a surprise; for the acid derived from it melted at 263° C. without decomposition, whereas Schultz's acid melted at 297° C, and Schmidt's acid melted at 303° C. with decomposition.

On reduction, Schultz's acid yields the corresponding diamino-acid : whereas Kenner's compound produces an internal dilactam with extraordinary readiness, so much so that an attempt to isolate the intermediate diamino-compound failed.

Kenner and Stubbings suggested that 6 : 6′-dinitrodiphenic acid existed in two forms which they believed were stereoisomers; and on this basis they explained the phenomena thus :—

[1] Kenner and Stubbings, *J.*, 1921, **119**, 593.

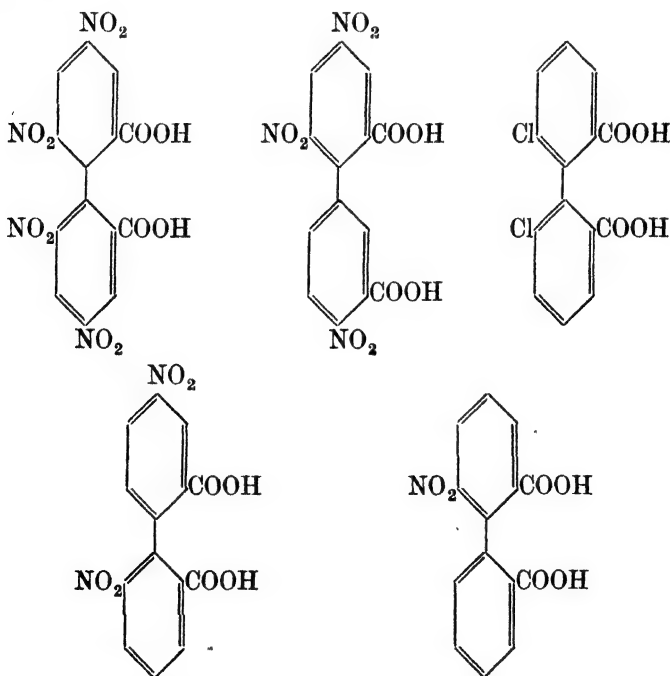
As Christie and Kenner [1] pointed out, there are at least three possible explanations for the behaviour of these diphenic acid derivatives. In the first place, both benzene rings may lie in one plane and there may be a hindrance to their free rotation about the bond which unites them. In these conditions, the isomerism would be akin to the *cis-trans* isomerism of maleic and fumaric acids, and no question of optical activity could arise. Secondly, the Kaufler hypothesis may be invoked; in which case the two isomeric acids would be represented thus :—

In this case, the *cis*-compound (A) possesses a plane of symmetry; whilst the *trans*-isomer (B) cannot be superposed on its mirror-image, and ought therefore to be capable of resolution into its antipodes. Finally, the two benzene rings may have a common axis, but the plane containing one ring may be perpendicular to the plane containing the second ring :—

In (C) the left-hand ring is supposed to lie in the plane of the paper, whilst the right-hand ring is assumed to lie in a plane inclined to the first at some angle other * than 90°. In this case the two nitro-groups and the two carboxyl radicles will lie at the corners of an irregular tetrahedron; and as an arrangement of this sort is not superposable upon its mirror-image, optical activity

[1] Christie and Kenner, *J.*, 1922, **121**, 614.

* If the two planes were perpendicular to each other, only one form of 6 : 6′-diphenic acid would be possible, since one model would be convertible into the other by mere rotation.

might be possible. There is a fourth possibility for the arrangement of the two rings, in which the model has neither an axis nor a plane of symmetry; but as it would demand more isomers than are known, it is unnecessary to consider it.

Christie and Kenner [1] found that Kenner's 6 : 6′-dinitrodiphenic acid yielded two brucine salts having different rotatory powers; so that the Kenner acid is clearly a mixture of two antipodic forms. This eliminated the possibility that the two benzene rings lie in one plane; and proved conclusively that either the Kaufler configuration or else the models suggested by Kenner and Christie must be relied on to account for the experimental results.

Further investigation extended this field of optical activity; and it was found that the following five acids [2] also existed in active forms :—

[1] Christie and Kenner, *J.*, 1922, **121**, 614.

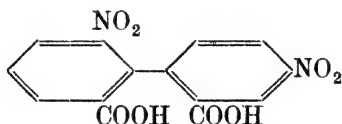
[2] *Ibid.*, 1922, **121**, 614; 1923, **123**, 779; Christie, James, and Kenner, *ibid.*, 1948; Christie, Holderness, and Kenner, *J.*, 1926, 671; Bell and Kenyon, *Chem. and Ind.*, 1926, **45**, 864.

At this point it may be well to forestall a possible criticism. It might be suggested that the benzene molecule is not necessarily a plane arrangement and that the optical activity observed by Christie and Kenner might have its origin in the asymmetry of a single benzene nucleus. This criticism can hardly be maintained in view of the failure of numerous attempts to resolve substituted benzenes into optically active components.[1]

The series of diphenyl acids had not yet yielded all its surprises with the discoveries which have just been described. A repetition [2] of the work of Schmidt and Kämpf on Schultz's dinitro-diphenic acid led to the discovery that instead of the 2 : 2′-dinitro-diphenyl which Schmidt and Kämpf believed they had obtained on driving off carbon dioxide, the actual product is 2 : 4′-dinitro-diphenyl. Thus Schultz's acid is not 6 : 6′-dinitro-diphenic acid, but is 4 : 6′-dinitro-diphenic acid with the structure shown below :—

NO_2

NO_2

COOH COOH

Thus Schultz's acid and the acid of Christie and Kenner are not stereoisomers but simply structure-isomers, differing from each other in the position of a nitro-group.

Like the 6 : 6′-dinitro-diphenic acid of Christie and Kenner, Schultz's acid has been shown to exist in active forms.[3]

3. *The Collapse of the Kaufler Hypothesis*

While this work was proceeding on the substituted diphenic acids, the original evidence upon which Kaufler had based his ideas was being subjected to revision, with the surprising result that all the data were found to be erroneous.[4]

The examples given in the first section of this chapter will be sufficient for the sake of illustration. The compound

[1] Le Bel, *Bull. Soc. chim.*, 1882, [2], **38**, 98 ; Lewkowitsch, *J.*, 1888, **53**, 791 ; V. Meyer and Lühn, *Ber.*, 1895, **28**, 2795 ; Jones and Kewley, *Proc. Camb. Phil. Soc.*, 1904, **12**, 122.

[2] Christie, Holderness, and Kenner, *J.*, 1926, 671.

[3] *Ibid.*, 1926, 671.

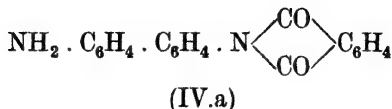
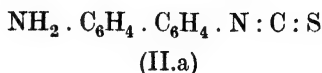
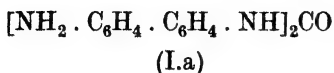
[4] Le Fèvre and Turner, *J.*, 1926, 2476 ; *J.*, 1928, 963 ; Dennett and Turner, *J.*, 1926, 1759 ; Le Fèvre, Moir, and Turner, *J.*, 1927, 2330 ; Brady and McHugh *J.*, 1923, **123**, 2047 ; Le Fèvre, *J.*, 1929, 733.

supposed to be carbonyl-benzidine (I.), turned out to be (I.a.); the thio-carbo-benzidine (II.) was shown to have the structure (II.a); the oxalyl derivative to which the formula (III.) had been ascribed, was proved to have a free amino-group; and the phthalyl compound has the constitution (IV.a) and not (IV).

$[NH_2 . C_6H_4 . C_6H_4 . NH]_2CO$ (I.a)

$NH_2 . C_6H_4 . C_6H_4 . N : C : S$ (II.a)

$NH_2 . C_6H_4 . C_6H_4 . N\langle{}^{CO}_{CO}\rangle C_6H_4$

(IV.a)

In none of these cases, as can be seen, do the two amino-groups of the benzidine molecule come into reaction simultaneously; and thus the phenomena which the Kaufler hypothesis was intended to explain do not exist in actual practice.

Williams and Weissberger [1] from an examination of the electrical moments of various diphenyl derivatives, inferred that in 4 : 4′-dichloro-diphenyl and 4 : 4′-dinitro-diphenyl, the rings are co-axial and cannot be inclined at an angle to each other; but in benzidine the molecule may have "a collapsed or folded structure." They are cautious to add, however, that their data are insufficient to establish the general truth of these conclusions.

One of the most convincing pieces of evidence against the Kaufler hypothesis has been brought forward by Barber and Smiles.[2] By oxidizing 2 : 2′-dithiol-diphenyl (I.), they obtained the diphenylene disulphide (II).

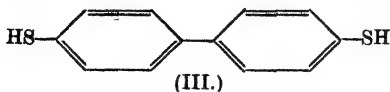
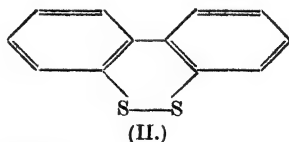
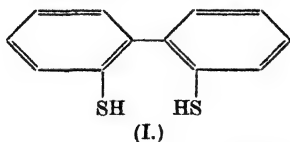
SH HS

(I.)

S—S

(II.)

HS— —SH

(III.)

[1] Williams and Weissberger, *J. Amer. Chem. Soc.*, 1928, **50**, 2332; compare Adkins, Steinbring, and Pickering, *ibid.*, 1924, **46**, 1917; Kühn and Albrecht, *Annalen*, 1927, **455**, 272.

[2] Barber and Smiles, *J.*, 1928, 1141.

Now obviously on the Kaufler hypothesis, the 4 : 4′-positions must be as near together in space as the 2 : 2′-positions ; and therefore 4 : 4′-dithiol-diphenyl (III.) should also give a disulphide on oxidation, if Kaufler's views be accurate. In practice, however, neither the 4 : 4′-dithiol-diphenyl nor the 3 : 3′-dithiol-diphenyl yield any such results. This seems absolutely convincing evidence on the subject.

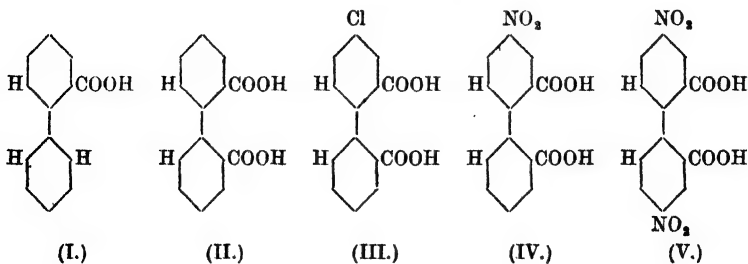
The net result of all this is perfectly plain. There is no evidence left which can be regarded as establishing the Kaufler hypothesis. All the evidence on which the hypothesis was first reared, turns out to be erroneous. And any fresh evidence which has real chemical value tells directly against Kaufler's views.

4. *Optical Activity in the Diphenyl Series*

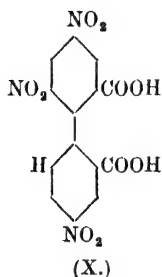
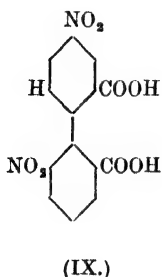
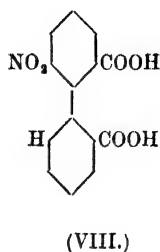
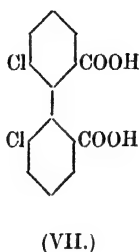
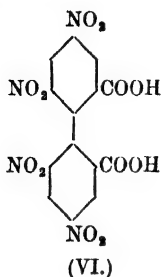
Though the Kaufler hypothesis is now out of court, it has left behind it the peculiar problem of optical activity among the substituted diphenic acids ; and at this stage it is desirable to consider the conditions under which this optical activity has been found to exist.

The first point which suggests itself is the relationship between structure and the occurrence of optical activity. Here the experimental material is sufficient to give a clue to the essential feature in the problem. The formulae of ten acids are shown below, with the benzene rings printed as simple hexagons to avoid complicating the pictures. The five formulae in the top line represent acids which have shown no sign of any capacity for resolution into optical antipodes ; whilst the five formulae in the lower lines represent acids which have been demonstrated to be racemic.

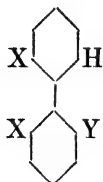
No resolution was attained with these acids :—

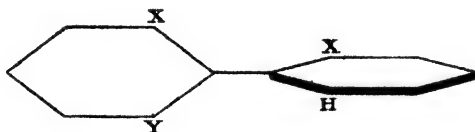
(I.) (II.) (III.) (IV.) (V.)

These acids are capable of resolution :—

Ring 1: NO_2 (top), NO_2, COOH; Ring 2: NO_2, COOH, NO_2 (bottom)	Ring 1: Cl, COOH; Ring 2: Cl, COOH	Ring 1: NO_2, COOH; Ring 2: H, COOH
(VI.)	(VII.)	(VIII.)

Ring 1: NO_2 (top), H, COOH; Ring 2: NO_2, COOH	Ring 1: NO_2 (top), NO_2, COOH; Ring 2: H, COOH, NO_2 (bottom)
(IX.)	(X.)

Inspection of these two sets of formulae reveals at a glance the difference between them. Taking the four positions which are *ortho* to the bond uniting the two phenyl nuclei, it is clear that optical activity does not occur unless *three out of the four* are occupied by certain substituents. If this condition be fulfilled, it is not necessary to have four *different* substituents attached to the diphenyl nucleus; it is sufficient if the two substituents in the same benzene ring are different from each other. Thus diphenic acid, (II.), has not been resolved; and, as the formula shows, it does not fulfil the condition about the three *ortho*-positions being filled by substituents. The dichloro-diphenic acid, (VII.), has been proved to exist in active forms; and in it the four *ortho*-hydrogens of diphenic acid have been replaced by substituents. Further, in (VII.) the diphenyl nucleus carries a pair of unlike substituents in each ring; but there are not four different substituents in all, so that the case is not parallel to that of the asymmetric carbon atom. Evidently a compound having the structure :—

X H

X Y

would fulfil the conditions required for the production of optical activity.

At this point it becomes clear that the two benzene rings in the active compounds cannot lie in the same plane ; because if they did so, the compound corresponding to the above formula would be symmetrical and hence unable to display optical activity. The hypothesis put forward by Christie and Kenner offers the easiest way out of the difficulty. If it be assumed that the planes of the two benzene rings are at right angles to each other,* then the following diagram will represent the conditions in the active molecules :—

Here the left-hand benzene ring is assumed to lie in the plane of the paper, whilst the right-hand one lies in a plane perpendicular to the paper. This model is not superposable on its mirror-image.

This model in itself is not sufficient, however ; for if there be free rotation about the bond adjoining the two nuclei, the two rings could swing into a co-planar configuration and symmetry would be established which would extinguish the optical activity of the compounds. In the above diagram, for example, if the right-hand ring were turned through 90°, it would fall into the plane of the paper and hence the model would become a plane figure.

To evade this objection, it is necessary to postulate that the free rotation of the rings around their common axis is inhibited by some factor or other, so that they can never become co-planar.

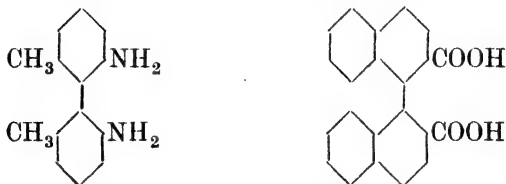
* This is the simplest assumption, though angles of inclination other than 90° are not excluded.

Various guesses [1] have been put forward as to the nature of the influence which prevents free rotation of the two nuclei. One of them depends upon a supposed "electrical repulsion" between the atom in the four *ortho*-positions; but it is difficult to see why this should break down in the case of diphenic acid itself, since the two similar carboxyl groups in it ought surely to exert a considerable mutual repulsion if there is anything in the idea at all.

A much more satisfactory explanation is obtained by going back to a purely mechanical idea of steric hindrance and taking into account the bulk of the substituent groups. When the model is built up from the usual tetrahedra, it is found that two bulky *ortho*-substituents in the one ring will interfere with the free rotation of the second ring, owing to collisions between them and the third *ortho*-substituent. If two of the groups are small, then free rotation is possible. This agrees with the case of the inactive diphenic acids, for there the two *ortho*-hydrogen atoms are not bulky enough to prevent the free rotation of the two rings about their common axis.

After the publication of this suggestion by Mills, many other diphenyl derivatives [2] were obtained in optically active forms :—

CH_3 NH_2 COOH

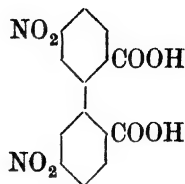
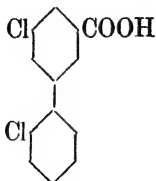
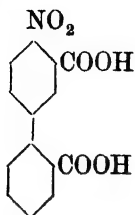
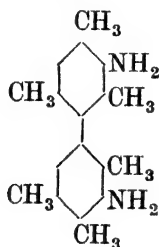
CH_3 NH_2 COOH

both of these fulfil the requirements of Mills's hypothesis.

Further support is lent to the steric hindrance view by negative results.[3] For example, in the three formulae shown below, it is clear that the substituents are not in positions which would

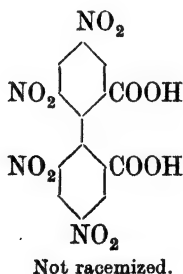
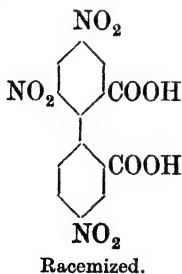
[1] Turner and Le Fèvre, *Chem. and Ind.*, 1926, **45**, 831; Mills, *ibid.*, 883, 905; Bell and Kenyon, *ibid.*, 864; *J.*, 1926, 3045.

[2] Meisenheimer, *Ber.*, 1927, **60**, [*B*], 1245; Kühn and Albrecht, *Annalen*, 1928, **464**, 91; **465**, 282; Kenner and Turner, *J.*, 1928, 2340; Kühn and Goldfinger, *Annalen*, 1929, **470**, 18; Mascarelli, *Gazzetta*, 1928, **58**, 627, Stanley and Adams, *Rec. trav. chim.*, 1929, **48**, 1035; Adams et al., *J. Amer. Chem. Soc.*, 1929, **51**, 630; 1930, **52**, 2070; 1931, **53**, 1575; 1932, **54**, 4434; 1933, **55**, 706; 1934, **56**, 1787; 1935, **57**, 1565; 1936, **58**, 587; 1939, **61**, 2825.

[3] McAllister and Kenner, *J.*, 1928, 1913; Kühn and Albrecht, *Annalen*, 1927, **455**, 272; Hyde and Adams, *J. Amer. Chem. Soc.*, 1928, **50**, 2499; Pufahl, *Ber.*, 1929, **62**, [*B*], 2817.

enable them sterically to hinder free rotation; and in practice these acids have not been resolved into active isomers.

The electrical character of the groups seems to play a very minor part—if any—in the phenomenon. This is shown by the fact that 3 : 3′-diamino-dimesityl

has been proved to be optically active,[1] although difference in "polarity" between the *ortho*-substituents is non-existent.

The effect of blocking the fourth *ortho*-position with a substituent [2] can be seen in the influence this exerts upon racemization :—

Racemized. Not racemized.

[1] Moyer and Adams, *J. Amer. Chem. Soc.*, 1929, **51**, 630.

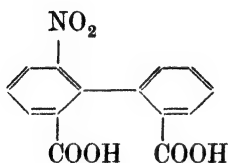
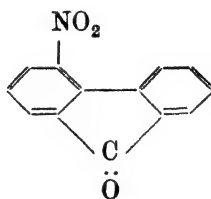
[2] Kühn and Albrecht, *Annalen*, 1927, **458**, 221; Maxwell and Adams, *J. Amer. Chem. Soc.*. 1938, **60**, 1411, 1489, 2179; 1939, **61**, 2182, 2825, 2828.

In addition to hydrogen atoms such other relatively small atoms as fluorine and groups like methoxyl permit free rotation of the benzene rings with the consequence that diphenyl derivatives containing these substituents in the 2 : 2′- or 6 : 6′-positions cannot be resolved into optical isomers.[1] This side of the problem has been elaborated and the restricting effect of different groups on the rotation of the benzene nuclei studied.[2]

Another interesting point arises when groups in the 2 : 2′ (or 6 : 6′) positions react to form a new ring. In these circumstances the optical activity of the diphenyl derivative disappears. Racemization cannot be called in to account for this as the optical isomers are stable under the reaction conditions. The most plausible explanation is that the new ring formation at the points 2 and 2′ forces the two parts of the diphenyl molecule into a co-planar arrangement. For example when the optically active diphenyl derivative (XI) was converted into its fluorenone (XII.) all attempts to resolve the fluorenone into optical isomers failed.[3]

NO_2 | COOH COOH

(XI.)

NO_2 | C | O

(XII.)

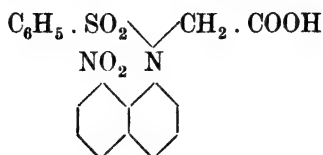
Other physical methods have been pressed into service to help to throw more light on the subject. X-ray and absorption spectra measurements and comparisons of the compounds have been interpreted as supporting the non-planar hypothesis.[4]

Even outside the diphenyl series, similar conditions seem to hold good, for the *peri*-naphthalene derivative :

[1] Adams et al., *J. Amer. Chem. Soc.*, 1932, **54**, 2973 ; 1933, **55**, 4219, 4225.

[2] *Idem, ibid.*, 1932, **55**, 4426, 4434 ; 1936, **58**, 587.

[3] Underwood and Kochmann, *J. Amer. Chem. Soc.*, 1924, **46**, 2069 ; Kühn and Jacob, *Ber.*, 1925, **58**, 1432 ; Bell and Robinson, *J.C.S.*, 1927, 2234 ; Meisenheimer and Höring, *Ber.*, 1927, **60**, 1425.

[4] Clark and Pickett, *J. Amer. Chem. Soc.*, 1931, **53**, 167 ; Pickett, *Nature*, 1933, **131**, 513 ; *Proc. Roy. Soc.*, 1933, **142** [A], 333 ; Pickett et al., *J. Amer. Chem. Soc.*, 1936, **58**, 2296, 2299 ; O'Shaughnessy and Rodebush, *ibid.*, 1940, **62**, 2906.

has been resolved,[1] though its activity proved to be slight. Here the free rotation of the benzene-sulphonyl-glycyl group is apparently hindered by the presence of the nitro-group.

Further, Stanley and Adams [2] have succeeded in resolving 2, 2′-dihydroxy-3, 3′-dicarboxy-1, 1′-dinaphthyl into its optical isomers, a result which shows that the phenomenon persists even in the dinaphthyl series.

As work proceeds the subject gets wider and wider and restricted rotation has been observed in dipyridyl, N-phenylpyrrole and N-dipyrryl derivatives.[3]

[1] Mills and Elliott, *J.*, 1928, 1291; Mills, *Trans. Faraday Soc.*, 1930, **26**, 431; Mills et al., *J.C.S.*, 1932, 2209; 1937, 274; 1939, 460; Adams et al., *J. Amer. Chem. Soc.*, 1940, **62**, 53; 1941, **63**, 1589, 2273; Jamison and Turner, *J.C.S.*, 1937, 1954; 1938, 1646; 1940, 264.

[2] Stanley and Adams, *Rec. trav. chim.*, 1929, **48**, 1035.

[3] Adams et al., *J. Amer. Chem. Soc.*, 1931, **53**, 374, 2253; 1932, **54**, 1977; 1934, **56**, 2089.

CHAPTER XII

SOME ASPECTS OF STEREOCHEMISTRY

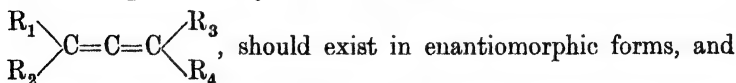
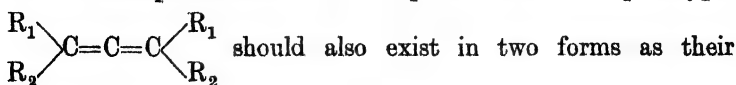
A.—Introductory

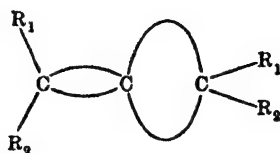
The well-tried methods of organic chemistry continue to increase our knowledge of stereochemistry, and the electronic theory is proving its worth in this field. Some cases of optically active sulphur and carbon compounds can be adequately explained by electronic structures where the older formulae fail.

Physical methods are being used increasingly to attack problems of molecular architecture ; the values obtained for the parachors of different groups, in a number of instances support the electronic formulae devised to explain the optical activity of certain compounds, and the application of X-ray and other physical methods of examination confirm the classification of compounds into groups having valency directions planar, tetrahedral and octahedral, so that our ideas in this connection have been made clearer and simplified. The tetrahedral distribution of valencies which proved so fruitful in the case of carbon is now found to explain equally well the configurations of a large number of the compounds of other elements as diverse as boron, nitrogen, sulphur, tin and zinc.

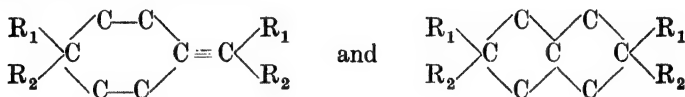
B.—The Allenes

1. *General*

It was predicted by Van't Hoff that allenes of the structure, $\begin{matrix} R_1 \\ R_2 \end{matrix} \!\!>\! C{=}C{=}C \!<\!\! \begin{matrix} R_3 \\ R_4 \end{matrix}$, should exist in enantiomorphic forms, and it was later pointed out that compounds of the simpler type, $\begin{matrix} R_1 \\ R_2 \end{matrix} \!\!>\! C{=}C{=}C \!<\!\! \begin{matrix} R_1 \\ R_2 \end{matrix}$ should also exist in two forms as their

mirror images are not superposable. When a molecular model of an allene of this latter type is built up it will readily be seen that the two structural halves of the molecule are not mirror images of one another. This molecule may be represented as

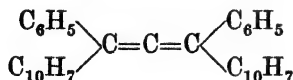
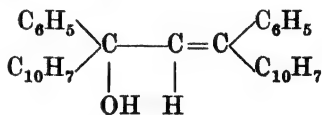
$$\begin{matrix} R_1 \\ \diagdown \\ C=C=C\langle^{R_1}_{R_2} \\ \diagup \\ R_2 \end{matrix}$$

where the radicles R_1 and R_2 on the left hand side are supposed to be in the plane of the paper, whilst R_1 and R_2 on the right hand side, lie above and below the paper respectively.

Although the compounds, stereochemically related to the allenes, of the structures

$$\begin{matrix} R_1 \\ R_2 \end{matrix}\rangle C\langle\begin{matrix} C-C \\ C-C \end{matrix}\rangle C=C\langle\begin{matrix} R_1 \\ R_2 \end{matrix} \quad \text{and} \quad \begin{matrix} R_1 \\ R_2 \end{matrix}\rangle C\langle\begin{matrix} C \\ C \end{matrix}\rangle C\langle\begin{matrix} C \\ C \end{matrix}\rangle C\langle\begin{matrix} R_1 \\ R_2 \end{matrix}$$

in which free rotation is also impossible, were early resolved into their optically active components, the allenes themselves until recently, defied resolution.

2. *The Resolution of the Allenes*

$\alpha\gamma$-Diphenyl-$\alpha\gamma$-di-1-naphthylallene (I) was found to be a suitable compound of this class to investigate [1]

$$\begin{matrix} C_6H_5 \\ C_{10}H_7 \end{matrix}\rangle C=C=C\langle\begin{matrix} C_6H_5 \\ C_{10}H_7 \end{matrix} \qquad \begin{matrix} C_6H_5 \\ C_{10}H_7 \end{matrix}\rangle \underset{OH}{\underset{|}{C}}-\underset{H}{\underset{|}{C}}=C\langle\begin{matrix} C_6H_5 \\ C_{10}H_7 \end{matrix}$$

(I.) (II.)

The corresponding substituted allyl alcohol of the structure (II) was readily dehydrated catalytically in the presence of *p*-toluene-sulphonic acid to give the racemic allene (I). The possibility of asymmetric catalysis was then considered and proved entirely successful with *d*-camphorsulphonic acid as the catalyst. The allyl alcohol (II) was heated in benzene solution with 1 per cent.

[1] **Maitland and Mills, *Nature*, 1935, 135, 994 ; *J.*, 1936, 987.**

of its weight of *d*-camphorsulphonic acid. The dehydration was complete in a short time, and after removal of the acid the strongly dextrorotatory solution contained the inactive allene and the dextro-isomer. These could be separated quite readily. The catalytic dehydration of the allyl alcohol was repeated in the presence of *l*-camphorsulphonic acid. Here the products were the inactive allene and the laevo-isomer.

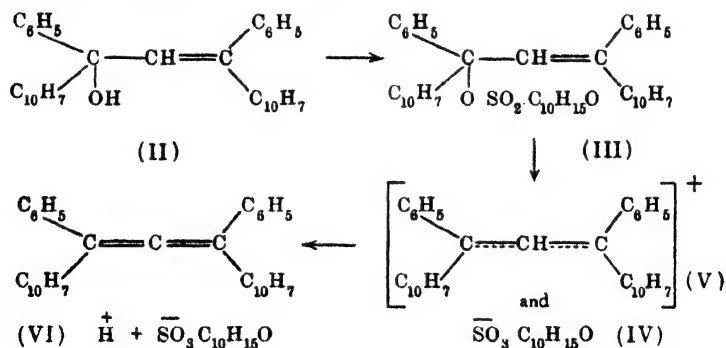
During the preparation of the allene (I) from the tertiary alcohol (II) by the action of camphorsulphonic acid, a purple coloration developed in the reaction mixture. This was thought to be due to the presence of a small quantity of the coloured (carbonium) form of the camphorsulphonate of the alcohol, since tetra-arylallyl alcohols resemble tri-arylcarbinols in their behaviour, and form coloured derivatives with acids. The intermediate formation of the alcohol camphorsulphonate suggests that the mechanism of the catalytic dehydration consists of the following stages: (*a*) esterification of the alcohol (II) by the camphorsulphonic acid, (*b*) dissociation of the resulting ester (III) into the camphorsulphonic ion (IV) and the coloured carbonium ion (V), (*c*) immediate decomposition of the carbonium ion into a hydrogen ion and the allene (VI).

$$(C_6H_5)(C_{10}H_7)C(OH)\text{—}CH{=}C(C_6H_5)(C_{10}H_7) \quad \text{(II)} \longrightarrow (C_6H_5)(C_{10}H_7)C(O\,SO_2{\cdot}C_{10}H_{15}O)\text{—}CH{=}C(C_6H_5)(C_{10}H_7) \quad \text{(III)}$$

$$\downarrow$$

$$\left[(C_6H_5)(C_{10}H_7)C\overset{\cdots}{=}CH\overset{\cdots}{=}C(C_6H_5)(C_{10}H_7)\right]^{+} \text{(V)} \quad \text{and} \quad \overset{-}{SO_3}\,C_{10}H_{15}O \quad \text{(IV)}$$

$$\longleftarrow$$

$$(C_6H_5)(C_{10}H_7)C{=}C{=}C(C_6H_5)(C_{10}H_7) \quad \text{(VI)} \quad \overset{+}{H} + \overset{-}{SO_3}C_{10}H_{15}O$$

Another allene derivative has been resolved into its active isomers so that the question of optical activity in these compounds is now definitely settled. The compound $\alpha\gamma$-diphenyl-γ-1-naphthylallene-α-carboxylic acid (VII) was first prepared many years ago, but attempts to resolve it into its active components by means of its salts with active bases failed.[1] This failure was

[1] Hann and Lapworth, *J.*, 1904, **85**, 1355; Lapworth and Wechsler, *ibid.*, 1910, **97**, 38.

due to the fact that the salts examined could not be crystallized. It has now been found that the glycollic acid ester (VIII) of this acid is well adapted to resolution. It crystallized readily, was easily purified, and its resolution by means of the brucine salt was accomplished without difficulty.[1] The parent acid (VII) and the glycollic acid ester (VIII) were prepared by the steps shown in the structural scheme below,

$$C_6H_5{-}CH{=}CH{-}C(=O){-}C_6H_5 \xrightarrow{HCN} C_6H_5{-}CH(CN){-}CH_2{-}C(=O){-}C_6H_5 \xrightarrow{\text{hydrolysis}} C_6H_5{-}CH(COOH){-}CH_2{-}C(=O){-}C_6H_5$$

$$\xrightarrow{C_2H_5OH} C_6H_5{-}CH(COOC_2H_5){-}CH_2{-}C(=O){-}C_6H_5 \xrightarrow[\text{and hydrolysis}]{C_{10}H_7MgBr} C_6H_5{-}CH(COOH){-}CH_2{-}C(OH)(C_6H_5){-}C_{10}H_7$$

$$\longrightarrow C_6H_5{-}\underset{|\;\;CO{-}{-}{-}{-}{-}{-}O\;\;|}{CH{-}CH_2{-}C}(C_6H_5)(C_{10}H_7)$$

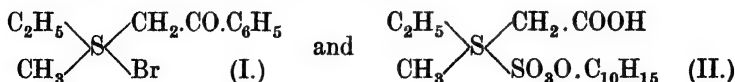
$$\xrightarrow{PCl_5 + C_2H_5OH} C_6H_5{-}CH(COOC_2H_5){-}CHCl{-}CCl(C_6H_5){-}C_{10}H_7 \xrightarrow[\text{(b) NaOH}]{\text{(a) pyridine}} \underset{\text{(VII)}}{(C_6H_5)(COOH)C{=}C{=}C(C_6H_5)(C_{10}H_7)}$$

$$\xrightarrow{PCl_5} (C_6H_5)(COCl)C{=}C{=}C(C_6H_5)(C_{10}H_7) \xrightarrow{\text{glycollic acid}} \underset{\text{(VIII)}}{(C_6H_5)(CO.OCH_2.COOH)C{=}C{=}C(C_6H_5)(C_{10}H_7)}$$

C.—The Asymmetry of the Sulphur Atom

1. *Introductory*

Compounds of sulphur such as

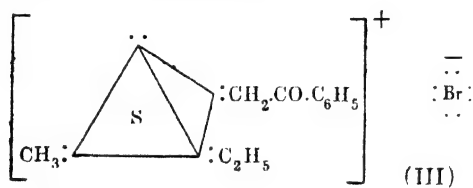
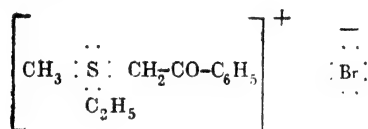
$$\begin{matrix} C_2H_5 \\ CH_3 \end{matrix}\!\!>\!S\!<\!\!\begin{matrix} CH_2.CO.C_6H_5 \\ Br \end{matrix} \quad (I.) \qquad \text{and} \qquad \begin{matrix} C_2H_5 \\ CH_3 \end{matrix}\!\!>\!S\!<\!\!\begin{matrix} CH_2.COOH \\ SO_3O.C_{10}H_{15} \end{matrix} \quad (II.)$$

and others with a strongly negative group in the molecule were isolated and shown to exist in optically active forms in the early days of the present century.[2] The space arrangement of the four

[1] Kohler, Walker, and Tishler, *J. Amer. Chem. Soc.*, 1935, **57**, 1743.

[2] Pope and Peachey, *J.*, 1900, **77**, 1072; Smiles, *ibid.*, 1174.

groups attached to the sulphur atom was assumed to be the same as in the case of carbon ; the sulphur atom being in the centre and the four groups at the corners of a tetrahedron. These substances, however, retain their optical activity on ionization, and one may conclude that the ionization of such a compound as the bromide (I) or camphorsulphonate (II) formulated above leaves the other three groups unchanged in their positions in the tetrahedral arrangement when the negative group on ionization vacates the fourth position. The ions of the bromide (I) may accordingly be formulated electronically as (III),

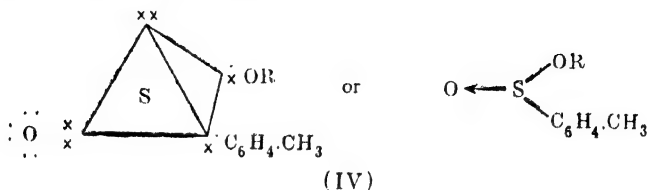
or more concisely

$$\left[CH_3 : \ddot{\underset{\cdot\cdot}{S}} : CH_2\text{-}CO\text{-}C_6H_5 \atop C_2H_5 \right]^+ \quad \overset{-}{:\ddot{\underset{\cdot\cdot}{Br}}:}$$

2. *The Sulphinates*

When we turn to the optically active sulphinic esters, sulphoxides and sulphilimines with only three groups attached to the sulphur atom we must further modify the older formulae such as $R—\overset{O}{\overset{/\!/}{S}}—O \, . \, C_6H_4 \, . \, CH_3$ and $NH_2 \, . \, C_6H_4—\overset{O}{\overset{\|}{S}}—C_6H_4 \, . \, CH_3$, which show oxygen linked by a double bond to sulphur. Asymmetry is not possible in such a molecule with two of the sulphur valencies attached to a single atom. The best way to formulate this type of molecule as asymmetric is, in accordance with modern theory, to regard the link between sulphur and oxygen as a single one in which the octet of oxygen is completed by the co-ordination of two electrons of the sulphur-atom. It must also be assumed that the three groups attached

to sulphur retain their places in a tetrahedral arrangement with the fourth point unoccupied. On this basis a sulphinate will have the structure (IV), in which two of the attachments are covalent and one a co-ordinate link.*

$:\ddot{O}:\,\times\times$ S (tetrahedron) $\times\,OR$, $\times\,C_6H_4.CH_3$ or $O \leftarrow S\langle^{OR}_{C_6H_4.CH_3}$

(IV)

The asymmetric sulphinate molecule, however, has a certain mobility as some of the esters show marked mutarotation, and when alkyloxy interchange is effected they undergo inversion with the production of the ester of opposite configuration. Aromatic sulphinic esters have been prepared by the interaction of the sodium sulphinate and an alcohol chlorocarbonate, or by the direct action of the sulphinyl chloride on the alcohol in the presence of potassium carbonate or pyridine to remove the hydrogen chloride formed. Other more complex esters, such as the *l*-menthyl and *l*-β-octyl *p*-toluene sulphinates, may then be prepared from the ethyl ester by heating with the menthyl or octyl alcohol under reduced pressure. Dextro- and laevo-ethyl *p*-toluenesulphinates were obtained by the action of heat on a mixture of two molecular proportions of the optically inactive ethyl *p*-toluenesulphinate with one of laevo-β-octanol. From the reaction mixture laevorotatory ethyl *p*-toluenesulphinate and laevorotatory β-octyl *p*-toluenesulphinate were isolated. The latter compound on alcoholysis yielded dextrorotatory ethyl *p*-toluenesulphinate. Other active alkyl sulphinates were isolated by similar methods.[1]

3. *The Sulphoxides*

From the theoretical considerations relating to the structures of optically active sulphinates it became evident that sulphoxides could be formulated in the same way and the new formula carried

* The valency electrons of the sulphur atom are represented as crosses, with the co-ordinate link between sulphur and oxygen represented by two crosses.

[1] Phillips, *J.*, 1925, **127**, 2552.

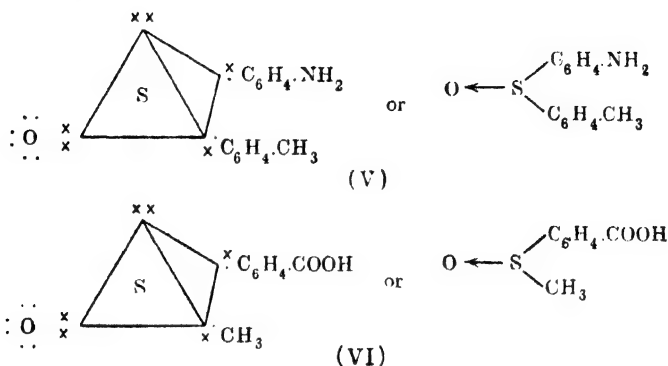
with it the implication that mixed sulphoxides should exist in optically active forms.

The two compounds 4′-amino-4-methyldiphenylsulphoxide (V.) and *m*-carboxyphenyl methylsulphoxide (VI) were therefore prepared. Their resolution into optically active isomers was successful.

$$O \leftarrow S\begin{matrix} C_6H_4.NH_2 \\ C_6H_4.CH_3 \end{matrix}$$

(V)

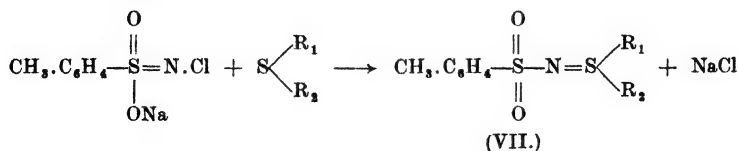
$$O \leftarrow S\begin{matrix} C_6H_4.COOH \\ CH_3 \end{matrix}$$

(VI)

dl-4′-Amino-4-methyldiphenyl sulphoxide (V.) was prepared by the interaction of aniline and *p*-toluenesulphinic acid. It readily combined with *d*-camphorsulphonic acid to give the salt, which on decomposition yielded the dextrorotatory sulphoxide. The laevorotatory isomer was isolated as the *l*-camphorsulphonate.[1]

4. *The Sulphilimines*

These substances (VII.) were formed by the condensation of dialkyl sulphides with chloramine-T. The reaction could be formulated as

$$CH_3.C_6H_4-\overset{O}{\overset{\|}{\underset{ONa}{\underset{|}{S}}}}=N.Cl + S\begin{matrix} R_1 \\ R_2 \end{matrix} \longrightarrow CH_3.C_6H_4-\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}-N=S\begin{matrix} R_1 \\ R_2 \end{matrix} + NaCl$$

(VII.)

It is known, however, from measurements of the molecular parachors of compounds containing a hexavalent sulphur atom linked to two oxygen atoms that the sulphur and oxygen atoms

[1] Harrison, Kenyon, and Phillips, *J.*, 1926, 2079.

are attached by co-ordinate bonds. In the structure of the chloramine-T molecule it is further suggested that the valencies of the trivalent nitrogen atom are made up of two covalencies and an electrovalency between the nitrogen and sodium atoms. The structure of chloramine-T can consequently be represented by formulae (VIII.)

$$CH_3-C_6H_4-\underset{\downarrow\atop O}{\overset{O\atop\uparrow}{S}}-\overset{-}{N}\begin{matrix}\diagup Cl \\ \cdots\overset{+}{Na}\end{matrix} \quad \text{or} \quad CH_3-C_6H_4 \times \underset{:\ddot{O}:}{\overset{:\ddot{O}:}{\ddot{S}}} \times N : Cl \quad :Na:$$

(VIII)

The constitutional formula of a sulphilimine is more readily deduced if the condensation of chloramine-T with the sulphide is assumed to occur in two stages. In the first stage the chloramine-T is considered to decompose into the active radicle (IX) by the separation of sodium and chlorine ions

$$CH_3\cdot C_6H_4-\underset{\downarrow\atop O}{\overset{O\atop\uparrow}{S}}-\overset{-}{N}\begin{matrix}\diagup Cl \\ \cdots\overset{+}{Na}\end{matrix} \longrightarrow CH_3-C_6H_4-\underset{\downarrow\atop O}{\overset{O\atop\uparrow}{S}} \times \ddot{N} + \overset{+}{Na} + \overset{-}{Cl}$$

(IX)

In the second stage of the reaction the nitrogen atom completes its octet at the expense of one of the two lone pairs of electrons present in the valency level of the sulphur atom of the sulphide (X). That is, a co-ordinate link is formed between the sulphur atom of the alkyl sulphide and the nitrogen atom of the chloramine-T radicle, as follows :

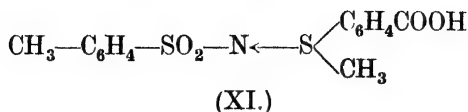
$$CH_3-C_6H_4-\underset{\downarrow\atop O}{\overset{O\atop\uparrow}{S}} \times \ddot{N} + \underset{R_2}{\overset{\times\times}{\times S\times}} R_1 \longrightarrow CH_3-C_6H_4-\underset{\downarrow\atop O}{\overset{O\atop\uparrow}{S}} \times \ddot{N} \times \underset{R_2}{\overset{\times\times}{S}} \times R_1$$

(X.)

Represented in this way, the linkage of the nitrogen and sulphur atoms of the sulphilimine is analogous with those of the sulphur atom to oxygen in the sulphinic esters and sulphoxides. Consequently the mixed sulphilimines should exist in optically

active forms. To test this view of the structure of the sulphilimines *m*-carboxyphenylmethylsulphine-*p*-toluene-sulphonylimine (XI) was prepared and examined.

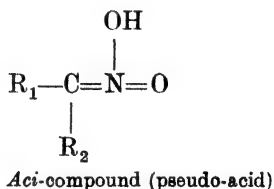
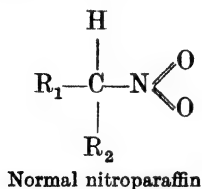
$$CH_3—C_6H_4—SO_2—N\leftarrow—S\begin{cases} C_6H_4COOH \\ CH_3 \end{cases}$$

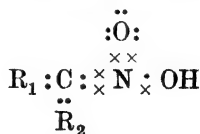
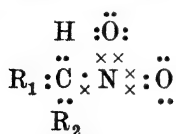
(XI.)

Its brucine salt on decomposition with dilute hydrochloric acid yielded the laevo-sulphilimine. The dextro-isomer was isolated as the cinchonidine salt and on decomposition had a specific rotation in agreement with that of the laevo-compound.[1]

5. *The Nitroparaffins*

It is well known that nitroparaffins with one or more hydrogen atoms attached to the carbon atom to which the nitro group is united can exist in two isomeric forms, the normal form and the *aci*-form.* The normal nitroparaffins and the corresponding *aci*-compound have been formulated as

$$R_1—\overset{\overset{\large H}{|}}{\underset{\underset{\large R_2}{|}}{C}}—N\begin{cases} O \\ O \end{cases} \qquad\qquad R_1—\overset{\overset{\large OH}{|}}{\underset{\underset{\large R_2}{|}}{C}}=N=O$$

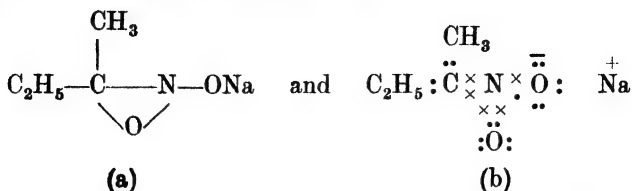
Normal nitroparaffin — *Aci*-compound (pseudo-acid)

Electronically these structures could be written down as

$$R_1 : \overset{H}{\underset{R_2}{\ddot{C}}} \overset{\bullet}{\times} \overset{:\ddot{O}:}{\overset{\times\times}{N}} \overset{\times}{\times} : \ddot{O} \qquad\qquad R_1 : \underset{R_2}{\ddot{C}} : \overset{\times}{\times} \overset{:\ddot{O}:}{\overset{\times\times}{N}} \overset{\bullet}{\times} OH$$

in which a co-ordinate link is shown between the nitrogen atom and one of the oxygen atoms. The discovery, however, that dextro-2-nitrobutane could be converted into an optically active sodium salt made a revision of these formulae for the *aci*-compounds necessary. The older structure, with a double bond

[1] Clarke, Kenyon, and Phillips, *J.*, 1927, 188.

* See Stewart, *Some Physico-Chemical Themes*, p. 96, for an account of this.

between carbon and nitrogen cannot be built up in enantiomorphous forms. The two possible structures which would explain the optical activity of the sodium salt of the nitrobutane are

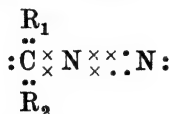
$$\begin{array}{c} CH_3 \\ | \\ C_2H_5—C——N—ONa \\ \diagdown O \diagup \\ \textbf{(a)} \end{array} \quad \text{and} \quad \begin{array}{c} CH_3 \\ \ddot{} \quad \bar{\ddot{}} \quad + \\ C_2H_5:C \overset{\times}{\underset{\times}{}} N \overset{\times}{.} O: \quad Na \\ \times\times \quad \ddot{} \\ :\ddot{O}: \\ (b) \end{array}$$

There are several objections to the structure (*a*) containing a carbazoxy ring. In the first place the existence of this cyclic formation has never been established, and secondly such a saturated structure does not indicate the great chemical activity of the *aci*-form of the nitroparaffins. The alternative structure (*b*) which shows carbon united to nitrogen by a co-ordinate link must, therefore, be accepted and this explanation of the asymmetry of the nitroparaffins brings them into line with the optically active sulphinic esters, sulphoxides and sulphilimines.[1]

In addition to 2-nitrobutane, 2-nitro-octane (I) and phenylcyanonitromethane (II.) have been isolated in the form of their optically active salts.[2]

$$\begin{array}{c} CH_3 \\ | \\ C_6H_{13}—C \leftarrow —NO_2Na \\ \text{(I.)} \end{array} \qquad \begin{array}{c} CN \\ | \\ C_6H_5—C \leftarrow —NO_2Na \\ \text{(II.)} \end{array}$$

The racemic compound of the latter was resolved into its optically active isomers in the usual way with brucine.

It is interesting to note that the asymmetry of the carbon atom bearing a diazo-group has been demonstrated, and can be explained by the electronic structure

$$\begin{array}{c} R_1 \\ \ddot{} \\ :C \overset{\times}{\underset{\times}{}} N \overset{\times\times}{\underset{\times}{}} \vdots N: \\ \ddot{} \\ R_2 \end{array}$$

in which a co-ordinate link between nitrogen and carbon is formulated.[3]

[1] Kühn and Albrecht, *Ber.*, 1927, **60**, 1297.

[2] Shriner and Young, *J. Amer. Chem. Soc.*, 1930, **52**, 3332; Mills, *Report of the British Association*, 1932, 37.

[3] Ray, *J. Amer. Chem. Soc.*, 1930, **52**, 3004.

6. *The Resolution of Stereoisomers by Selective Adsorption*

During the past forty years attempts have been made to separate the active components of racemic compounds by selective adsorption without any great success.[1] Very small partial resolutions have been effected and some materials having faint activity have been isolated.[2] In recent years, however, the technique of adsorption has been refined to such an extent by the introduction of the Tswett's chromatographic procedure that it is now possible to isolate the optically pure components from a racemic mixture. It reflects little credit on the initiative and perspicacity of chemists that Tswett's invention, introduced in 1906, remained practically unnoticed for twenty-five years.

There are two ways in which chromatography can be used to separate the active components of a racemic compound. In the first method a solution of the racemic substance is passed through a column of optically active adsorbent such as lactose or quartz. In the second method the racemic compound is first allowed to interact with a suitable dextro- (or laevo-) compound and the resulting mixture of *d-d-* and *d-l-*compounds fractionated chromatographically on an adsorption column of such a material as alumina, which has no stereo-orientation. The resolution of *dl-p-*phenylene*bis*iminocamphor $(C_{10}H_{14}O : N^{\cdot})_2C_6H_4$, is a very good illustration of the first method. This compound in a benzene-petroleum mixture was allowed to flow through a column of *d-*lactose. As soon as the pale yellow adsorbed layer occupied a sufficient length of the adsorption tube it was developed by washing with the pure solvent mixture until it expanded to the foot of the tube. The contents of the tube were extruded and the top and bottom sections of the column separated. It was found that the *d-*iminocamphor was more strongly adsorbed on the *d-*lactose than the *l-*isomer. Consequently the product obtained from the top section of the column was dextrorotatory and that from the lower section laevorotatory. Solutions of these partially resolved fractions were submitted to a further percolation through lactose and dextro- and laevo-fractions showing

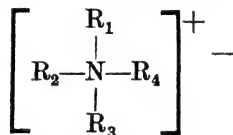
[1] Willstätter, *Ber.*, 1904, **37**, 3758; Porter and Ihrig, *J. Amer. Chem. Soc.*, 1923, **45**, 1990; Borde and Adams, *ibid.*, 1926, **48**, 2193, 2202.

[2] Tsuchida, Kobayashi, and Nakamura, *Bull. Chem. Soc. Japan*, 1936, II, 38; Ingerson and Adams, *J. Amer. Chem. Soc.*, 1922, **44**, 2930.

enhanced rotations obtained. Optically pure *l-p*-phenylene-*bis*iminocamphor was finally isolated after further adsorptions.[1] The second method of separating the components of a racemic compound has been employed in the following way. Racemic mandelic acid was converted into its laevo-menthyl esters, which were dissolved in light petroleum and passed through a column of alumina. The column was then treated with some of the pure solvent. An upper fraction of the alumina was then extracted with an alcohol-benzene mixture, and the solvent then evaporated off. The solid residue was dissolved in ethyl alcohol and from observation of the optical rotation of this solution it was estimated that the solid residue obtained from the alumina contained 58·5 per cent. *l*-menthyl *l*-mandelate and 41·5 per cent. of the *l-d*-isomer.[2]

7. *Conclusion*

The discovery of the sulphinate and nitroparaffin type of asymmetry described in this chapter has brought about a considerable change of our ideas on the configurational stability of the compounds of tri-covalent sulphur and carbon. On the other hand, although many nitrogen compounds of the type

$$\left[\begin{array}{ccc} & R_1 & \\ & | & \\ R_2 - & N & - R_4 \\ & | & \\ & R_3 & \end{array}\right]^{+} -$$

have been resolved, no tri-covalent compounds of nitrogen, such as the amines have been resolved into their optically active isomers, pointing to great configurational instability in this class of compound.[3]

[1] Henderson and Rule, *Nature*, 1937, **141**, 917; *J.C.S.*, 1939, 1568; Karagunis and Coumoulos, *Praktika*, 1938, **13**, 414; *Nature*, 1938, **142**, 162.

[2] Jamison and Turner, *J.*, 1942, 611.

[3] Mills, *J.*, 1943, 194.

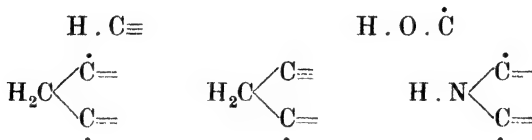
CHAPTER XIII

NEW ORGANO-ALKALI COMPOUNDS

1. *Introductory*

Among the most familiar phenomena of organic chemistry is the displacement of a hydrogen atom by sodium. Acetylene, acetic acid, malonic ester, cyanacetic ester, cyclopentadiene, biuret, and pyrrol—to name only a few compounds—contain replaceable hydrogen atoms. In these cases, it appears that the property depends upon the accumulation of residual affinity in the immediate neighbourhood of the replaceable hydrogen; for one or other of the following groupings is always present:

$$H.C\equiv \qquad\qquad H.O.\dot{C}$$

$$H_2C\left\langle\begin{matrix}\dot{C}= \\ \underset{\bullet}{C}=\end{matrix}\right. \qquad H_2C\left\langle\begin{matrix}C\equiv \\ \underset{\bullet}{C}=\end{matrix}\right. \qquad H.N\left\langle\begin{matrix}\dot{C}= \\ \underset{\bullet}{C}=\end{matrix}\right.$$

Where a choice is possible, the sodium atom on entering the molecule appears to attach itself by preference to a non-carbon atom.

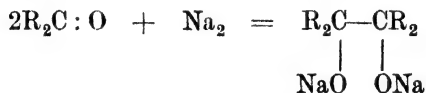
On the other hand, many of the polyvalent metals are known to form alkyl derivatives which contain no structures similar to those shown above; for in their case there is a direct attachment of alkyl and aryl radicles to the metallic atom, as in zinc methyl, $Zn(CH_3)_2$, and mercury diphenyl, $Hg(C_6H_5)_2$. It is, however, only in quite recent times that a study has been made of the simple alkyl and aryl derivatives of lithium, sodium, and potassium; for the experimental difficulties which stood in the way were found to be considerable.

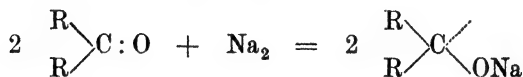
As far back as 1858, Wanklyn[1] observed that metallic sodium dissolves in zinc ethyl with the formation of a double

[1] Wanklyn, *Annalen*, 1858, **107**, 125; **108**, 168; 1859, **111**, 234; 1866, **140**, 211.

compound. A year later, Buckton [1] studied the action of sodium upon the mercury alkyl derivatives; but owing to the readiness with which the products were oxidized, he was unable to obtain definite results. The work of Schorigin [2] brought some fresh points to light; but still the experimental difficulties stood in the way of fuller knowledge. It was left to later investigators with improved technique to clear up the field.[3]

A very similar delay is found, as will be seen later, in the history of the metal-ketyls, which are prepared by the action of sodium upon certain ketones. When the alkali metals act upon ketonic compounds, the reaction is found to follow one of the three following courses. (1) An alkali compound may be formed, with the evolution of hydrogen. This takes place when the ketone is capable of enolization; and it is not confined to cases in which the group $—CO—CH_2—CO—$ is present; for acetone itself has been found to react with sodium in the form $CH_2 : C(OH).CH_3$. Reactions of this type may lead to very complex products; for condensations may set in, and there may be reduction due to the liberated hydrogen. (2) The alkali metal may be taken up by the ketone without elimination of hydrogen, yielding reaction-products from two molecules of the ketone:

$$2R_2C:O + Na_2 = \begin{matrix} R_2C—CR_2 \\ | \quad\ \ | \\ NaO \quad ONa \end{matrix}$$

Finally, (3) the alkali metal may attack a single molecule of the ketone, without the evolution of hydrogen, forming a metal-ketyl containing a trivalent carbon atom:

$$2 \begin{matrix} R \\ R \end{matrix}\!\!>\!C:O + Na_2 = 2 \begin{matrix} R \\ R \end{matrix}\!\!>\!C\!\!\begin{matrix} / \\ \backslash ONa \end{matrix}$$

Cases (2) and (3) are observed only when the ketone is incapable of enolization. Our present knowledge is not sufficient to

[1] Buckton, *Annalen*, 1859, **112**, 222.

[2] Schorigin, *Ber.*, 1908, **41**, 2711; 1910, **43**, 1931.

[3] The fullest account of this work, including details not published elsewhere, is to be found in Schlenk's article in Houben-Weyl's *Die Methoden der organischen Chemie*, Band IV., pp. 957 ff. (1924). In the journals, see Schlenk and his collaborators, *Ber.*, 1914, **47**, 473; 483, 1664; 1916, **49**, 608; 1917, **50**, 262; 1922, **55**, 2285.

enable us to predict whether a non-enolizable ketone will yield by preference reaction (2) or reaction (3).

2. *The Alkali-alkyls*

When metallic lithium or sodium acts upon an alkyl derivative of mercury, the reaction [1] takes the following course:

$$HgR_2 + Na_2 = 2Na . R + Hg$$

In practice,[2] however, the matter is by no means simple, as special precautions have to be observed owing to the great sensitiveness of the alkali-alkyls.

For example, in the case of sodium methyl, $CH_3 . Na$, metallic sodium in a finely-divided state is covered with absolutely dry ligroin in a special apparatus through which thoroughly-dried nitrogen is passed to exclude all traces of air and moisture. The proper quantity of mercury methyl is then added, and the apparatus is sealed off from contact with the air. After the mixture has stood for some days at a temperature of 65° C., a small amount of white powder separates out and the particles of sodium become covered with a yellowish crust. At the same time, the liberated mercury forms an amalgam with the unaffected sodium. In order to separate the powdery sodium methyl from the amalgam, the apparatus is placed in a freezing-mixture, which has the effect of loosening the deposit of alkyl derivatives from the surface of the sodium particles; and thereafter by decantation and filtration in a special apparatus a separation of the two materials is attained.

In the preparation of lithium methyl, $Li . CH_3$, advantage is taken of the fact that it is insoluble in a mixture of petroleum ether and petroleum benzine, whereas lithium ethyl is soluble. A solution of lithium ethyl in petroleum benzine is mixed with a solution of mercury dimethyl in petroleum ether, and the lithium methyl formed by double decomposition is precipitated:

$$\underset{\text{Soluble.}}{2Li . C_2H_5} + \underset{\text{Soluble.}}{Hg(CH_3)_2} = \underset{\text{Insoluble.}}{2Li . CH_3} + \underset{\text{Soluble.}}{Hg(C_2H_5)_2}$$

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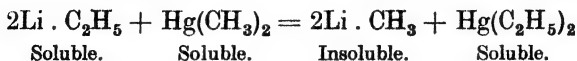
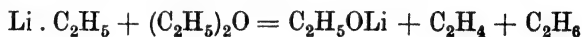

[1] Buckton, *Annalen*, 1859, **112**, 222; Acree, *J. Amer. Chem. Soc.*, 1903, **29**, 590; Schorigin, *Ber.*, 1908, **41**, 2711; 1910, **43**, 1931; Schlenk and Holtz, *Ber.*, 1917, **50**, 262.

[2] See Schlenk's article in Houben-Weyl's *Methoden der organischen Chemie*, IV., p. 959 (1924).

Here also, of course, all the operations are conducted in a dry nitrogen atmosphere.

Sodium methyl is generally obtained in an impure state, contaminated with some coloured material. Lithium ethyl has been prepared quite pure. It forms transparent crystals melting in a nitrogen atmosphere at 95° C. In the absence of air it can be distilled without much decomposition. It is soluble in benzene and the low-boiling hydrocarbons. Ether decomposes it readily according to the following equation :

$$Li \,.\, C_2H_5 + (C_2H_5)_2O = C_2H_5OLi + C_2H_4 + C_2H_6$$

Phenol acts upon sodium methyl with the production of sodium phenate.

In order to observe the reactions of the sodium alkyls it is not necessary to isolate them in a pure state. By mixing together metallic sodium, the proper mercury alkyl, and the third substance upon which the sodium alkyl is to act, it is possible to obtain the same end-product as would be produced by the direct action of the sodium alkyl upon the third substance. In this way [1] from benzophenone, sodium, and mercury diethyl, it was found that diphenyl-ethyl-carbinol, $(C_6H_5)_2C(Et).OH$, was formed. Benzoic ester with sodium and mercury diethyl gave diethyl-phenyl-carbinol, $C_6H_5 \,.\, C(Et)_2 \,.\, OH$. The action of carbon dioxide upon a mixture of sodium and mercury di-*iso*amyl yielded *iso*butyl-acetic acid, $(CH_3)_2CH \,.\, CH_2 \,.\, CH_2 \,.\, COOH$. When benzene or its homologues are used as solvents in these reactions, complications arise, for the hydrocarbons themselves are attacked during the process. It is noteworthy that homologues of benzene are more susceptible in the side-chain than in the nucleus. Thus when toluene is used as a solvent in the reaction between sodium, carbon dioxide, and mercury diethyl, a certain quantity of phenyl-acetic acid is produced. Sodium ethyl reacts with carbon monoxide [2] to yield various products, among which is a ketone.

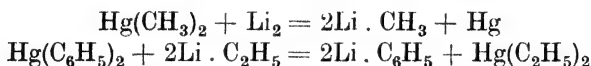
In view of further facts which will be mentioned later in this chapter, it should be noted that the alkali-alkyls when pure are colourless substances.

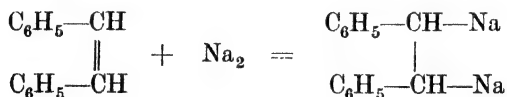
[1] Schorigin, *Ber.*, 1908, **41**, 2711.
[2] Wanklyn, *Annalen*, 1866, **140**, 211 ; Schlubach, *Ber.*, 1919, **52**, 1910.

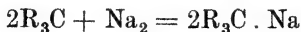
3. *The Alkali-aryls*

The aryl derivatives of the alkali metals have been obtained by four different methods: (1) by the action of mercury aryl derivatives upon metallic sodium; (2) by the double decomposition of an alkali-alkyl with a mercury-aryl derivative; (3) by the addition of metallic atoms to ethylenic linkages; and (4) by the union of alkali metals with free radicles of the triphenylmethyl type.

The applications of the first two methods to the preparation of lithium phenyl are illustrated by the following equations:—

$$Hg(CH_3)_2 + Li_2 = 2Li \cdot CH_3 + Hg$$
$$Hg(C_6H_5)_2 + 2Li \cdot C_2H_5 = 2Li \cdot C_6H_5 + Hg(C_2H_5)_2$$

In the third method, the process employed is as follows.[1] The ethylene derivative, such as stilbene or tetraphenyl-ethylene, is dissolved in dry ether and mixed with sodium in a sealed tube from which air has been excluded. After having been shaken for a time which varies from hours to days, the liquid becomes coloured; and eventually the sodium derivative separates out in the form of a fine powder, which is isolated with special precautions. In the case of stilbene, the addition takes place as shown below:

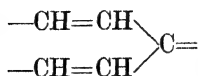
$$\begin{matrix} C_6H_5-CH \\ \| \\ C_6H_5-CH \end{matrix} + Na_2 = \begin{matrix} C_6H_5-CH-Na \\ | \\ C_6H_5-CH-Na \end{matrix}$$

The fourth method [2] consists in allowing an ethereal solution of the triarylmethyl to act upon sodium powder. Rather unexpectedly, triphenylmethyl itself is the only member of the series which up to the present has been found to react with difficulty; its homologues readily react thus:

$$2R_3C + Na_2 = 2R_3C \cdot Na$$

When sodium amalgam is used instead of metallic sodium, triphenylmethyl gives the normal reaction smoothly.

It seems of interest to point out certain factors which have a bearing upon the production of alkali-aryls by the third and fourth methods.

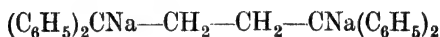
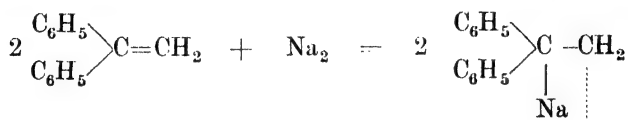
[1] Schlenk and Appenrodt, *Ber.*, 1914, **47**, 473.
[2] Schlenk and Marcus, *Ber.*, 1914, **47**, 1664.

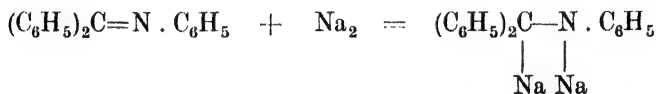
In order that sodium may act upon a double linkage, one of two conditions must be fulfilled. The carbon atoms united by the ethylenic bond must be joined directly to benzene nuclei, as in stilbene or anthracene ; or else the grouping

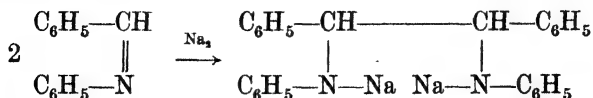
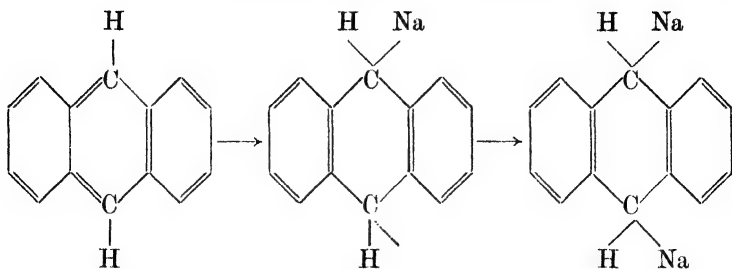
$$\begin{matrix} —CH{=}CH \searrow \\ \quad\quad\quad\quad C{=} \\ —CH{=}CH \nearrow \end{matrix}$$

must be present in the structure of the reacting molecule. For example, diphenyl-ethylene reacts as shown below, only the carbon atom carrying the two phenyl groups being attacked :

$$2 \begin{matrix} C_6H_5 \\ C_6H_5 \end{matrix} \!\!> C{=}CH_2 \;+\; Na_2 \;=\; 2 \begin{matrix} C_6H_5 \\ C_6H_5 \end{matrix} \!\!> \underset{\displaystyle Na}{\underset{|}{C}} —CH_2$$

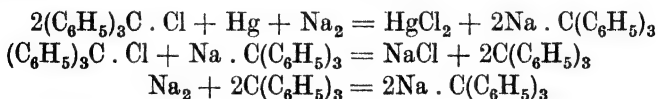
$$\swarrow$$

$$(C_6H_5)_2CNa—CH_2—CH_2—CNa(C_6H_5)_2$$

It is noteworthy that when these conditions are fulfilled, the carbon-nitrogen double bond is attacked by sodium ; but there it is essential to have two phenyl radicles attached to the carbon atom. Thus benzophenone-anil yields a disodium derivative :

$$(C_6H_5)_2C{=}N\,.\,C_6H_5 \;+\; Na_2 \;=\; (C_6H_5)_2\underset{\displaystyle Na}{\underset{|}{C}}—\underset{\displaystyle Na}{\underset{|}{N}}\,.\,C_6H_5$$

whereas the anil of benzaldehyde takes up one atom of sodium at the nitrogen atom and then two molecules of this product unite together, as in the case of diphenyl-ethylene which was mentioned above.

$$2 \begin{matrix} C_6H_5—CH \\ \| \\ C_6H_5—N \end{matrix} \xrightarrow{Na_2} \begin{matrix} C_6H_5—CH & ———— & CH—C_6H_5 \\ | & & | \\ C_6H_5—N—Na & & Na—N—C_6H_5 \end{matrix}$$

The case of anthracene is interesting on account of the fact that the addition-reaction proceeds in two stages which are marked by colour-changes in the solution.

Initially colourless, the solution first turns deep-blue when one sodium atom is attached ; and with the entry of the second sodium atom it goes violet.*

Turning now to the fourth method of preparing the alkali-aryls, it has already been pointed out that only in the case of triphenylmethyl itself was any difficulty encountered in the application of the general method. The source of trouble lies in the fact that, in presence of metallic sodium, triphenylmethyl is readily isomerised into the hydrocarbon [1] discovered by Ullmann and Borsum, $(C_6H_5)_3C—C_6H_4—CH(C_6H_5)_2$; and this naturally lowers the yield of alkali-aryl which it is possible to obtain. By substituting sodium amalgam for metallic sodium this is avoided ; and if that be done, then there is no need to make a separate preparation of the triphenylmethyl, since it becomes unnecessary. Triphenyl-chloro-methane is used as a starting-point. On treatment with sodium amalgam, the chlorine atom is removed by the mercury of the amalgam and its place is taken by a sodium atom. The sodium triphenylmethyl thus produced reacts with the remaining triphenyl-chloro-methane to form triphenylmethyl which, with the excess of sodium, then gives the sodium triaryl :

$$2(C_6H_5)_3C\ .\ Cl + Hg + Na_2 = HgCl_2 + 2Na\ .\ C(C_6H_5)_3$$
$$(C_6H_5)_3C\ .\ Cl + Na\ .\ C(C_6H_5)_3 = NaCl + 2C(C_6H_5)_3$$
$$Na_2 + 2C(C_6H_5)_3 = 2Na\ .\ C(C_6H_5)_3$$

Only a brief survey of the properties of the alkali-aryls can be given here ; but it will be found that they present certain peculiarities of considerable interest.

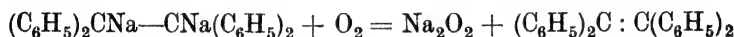
* This colour change is hard to explain on ordinary views of the relations between colour and constitution. Compare the case of the disodium derivative of benzophenone on p. 286.

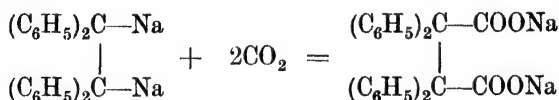
[1] Ullmann and Borsum, *Ber.*, 1902, **35**, 2877.

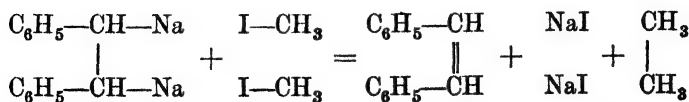
Lithium phenyl, $Li . C_6H_5$, resembles the alkali-alkyls in being a white crystalline powder. It reacts violently with water. When burned in air, it shows a *yellow* flame, quite unlike the usual flame-colour of lithium.

When the metallic atom is not directly attached to the phenyl nucleus, a complete change in properties is observed. Sodium benzyl, $Na . CH_2 . C_6H_5$, is strongly coloured red; sodium diphenylmethyl, $Na : CH(C_6H_5)_2$, and sodium triphenylmethyl, $Na . C(C_6H_5)_3$, are also deeply coloured compounds. Now an examination of electrical conductivity in ethereal solution proves that the colourless alkali derivatives are non-electrolytes, whereas the coloured * alkali-aryls conduct the current. This cannot fail to recall to mind the behaviour of triphenylmethyl and the carbonium salts.

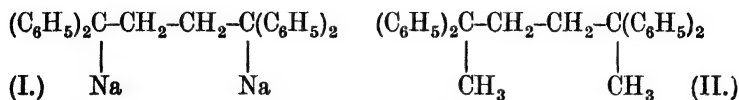
The disodium derivatives, obtained by acting upon double bonds with metallic sodium, are reactive like the simpler materials. In the presence of air, they regenerate the original compounds from which they were prepared,

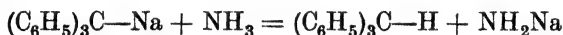
$$(C_6H_5)_2CNa—CNa(C_6H_5)_2 + O_2 = Na_2O_2 + (C_6H_5)_2C : C(C_6H_5)_2$$

though in some cases further decomposition ensues. Water hydrolyses them instantly, with the production of an alkali hydroxide and regeneration of the original material. Carbon dioxide acts with the formation of the salts of carboxylic acids

$$\begin{matrix} (C_6H_5)_2C—Na \\ | \\ (C_6H_5)_2C—Na \end{matrix} + 2CO_2 = \begin{matrix} (C_6H_5)_2C—COONa \\ | \\ (C_6H_5)_2C—COONa \end{matrix}$$

A rather curious result is observed when alkyl halides interact with these disodium derivatives. Instead of a replacement of sodium atoms by alkyl groups—which might be expected—a regeneration of the original compound is observed, accompanied by the production of a new hydrocarbon.

$$\begin{matrix} C_6H_5—CH—Na \\ | \\ C_6H_5—CH—Na \end{matrix} + \begin{matrix} I—CH_3 \\ \\ I—CH_3 \end{matrix} = \begin{matrix} C_6H_5—CH \\ \| \\ C_6H_5—CH \end{matrix} + \begin{matrix} NaI \\ \\ NaI \end{matrix} + \begin{matrix} CH_3 \\ | \\ CH_3 \end{matrix}$$

* The *colourless* alkali phenyls are not electrolytes.

In the case of the abnormal disodium derivatives which have the sodium atoms in the 1, 4- instead of the 1, 2-positions, methyl iodide acts normally by replacing the sodium atoms by methyl radicles. Thus the disodium derivative (I.), obtained from diphenyl-ethylene, gives rise to 2, 2, 5, 5-tetraphenyl-hexane (II.).

$$\underset{\text{(I.)}}{} (C_6H_5)_2\underset{|\atop Na}{C}-CH_2-CH_2-\underset{|\atop Na}{C}(C_6H_5)_2 \qquad (C_6H_5)_2\underset{|\atop CH_3}{C}-CH_2-CH_2-\underset{|\atop CH_3}{C}(C_6H_5)_2 \quad \text{(II.)}$$

The reactions of the sodium triaryls [1] are of special interest. There appears to be a close parallelism between sodium triphenylmethyl and the Grignard reagent, though the sodium compound is much more active than the magnesium derivative. It should be noted that sodium triphenylmethyl is very readily converted into triphenylmethane. When the sodium derivative acts upon any substance containing a hydroxyl radicle, triphenylmethane is formed ; and this sodium triphenylmethyl, like the Grignard reagent, is a sensitive reagent for the detection of enolic hydroxyl groups. Ammonia acts in a similar manner on sodium triphenylmethyl :

$$(C_6H_5)_3C—Na + NH_3 = (C_6H_5)_3C—H + NH_2Na$$

A few illustrations will bring to light the close resemblance between the Grignard reactions and those of sodium triphenylmethyl. When carbon dioxide acts on sodium triphenylmethyl, the sodium salt of triphenyl-acetic acid, $(C_6H_5)_3C . COONa$, is formed. With sulphur dioxide, an exactly analogous reaction leads to the production of a sulphinate, $(C_6H_5)_3C . SO_2 . Na$. Alkyl halides replace the sodium atom of the sodium triphenylmethyl by an alkyl radicle. When an aldehyde cannot yield a hydroxyl group by enolization, it reacts normally with sodium triphenylmethyl. For instance, formaldehyde yields $(C_6H_5)_3C.CH_2OH$, and benzaldehyde gives $(C_6H_5)_3C.CHOH.C_6H_5$. If the aldehyde, however, can be isomerised into an enolic variety, then triphenylmethane is formed. A similar state of affairs is found with the esters. When there is a hydrogen atom attached to the carbon atom carrying the carbethoxy-group,

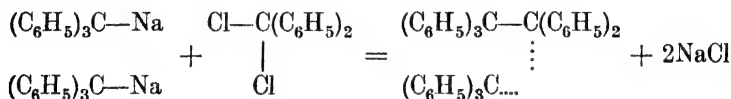
[1] Schlenk and others, *Ber.*, 1914, **47**, 1664 ; 1916, **49**, 608 ; 1922, **55**, 2285 ; Schlubach, *Ber.*, 1919, **52**, 1910.

the reaction proceeds with the formation of triphenylmethane. For instance, acetic ester behaves as if it had the structure (I.); whereas benzoic ester (II.) obviously cannot furnish an enolic form, and the product in its case is β-benzopinacoline, $(C_6H_5)_3C . CO . C_6H_5$.

$$\text{(I.)}\quad CH_2{=}C\begin{cases}OEt\\OH\end{cases}\qquad\qquad \text{(II.)}\quad C_6H_5{-}C\begin{cases}{=}O\\OEt\end{cases}$$

This benzopinacoline is formed also by the action of sodium triphenylmethyl upon benzoyl chloride, the reaction being a simple elimination of sodium chloride.

Two peculiar reactions of sodium triphenylmethyl deserve special attention. When it reacts with benzophenone chloride, a mixture of triphenylmethyl and pentaphenylethyl is formed:

$$\begin{matrix}(C_6H_5)_3C{-}Na & & Cl{-}C(C_6H_5)_2 & & (C_6H_5)_3C{-}C(C_6H_5)_2 & \\ & + & | & = & \vdots & + 2NaCl\\ (C_6H_5)_3C{-}Na & & Cl & & (C_6H_5)_3C\ldots & \end{matrix}$$

It appears as if octaphenyl-propane were formed and then dissociated into the two radicles, each of which contains trivalent carbon.

The most interesting product obtained from sodium triphenylmethyl is prepared as follows.[1] Sodium triphenylmethyl is mixed in ethereal solution with tetramethyl ammonium chloride. Excess of ammonium salt is removed by solution in pyridine and precipitation with ether. Red crystals are obtained, which have a composition corresponding to the formula $(C_6H_5)_3C{-}N(CH_3)_4$. The compound, as can be seen by inspection, has *five* alkyl groups attached to a nitrogen atom. On testing the material's conducting power in pyridine solution, it was found to be an electrolyte. Thus for the first time a compound has been obtained in which an aryl radicle acts as the anion of an ammonium derivative.

By parallel methods, the compound $(C_6H_5)_2N{-}N(CH_3)_4$ has been prepared from potassium diphenylamine and tetramethylammonium chloride; and this diphenylamino-tetramethylammonium also yields ions in pyridine solution.

[1] Schlenk and Holtz, *Ber.*, 1916, **49**, 608; compare Kraus and Kawamura, *J. Amer. Chem. Soc.*, 1923, **45**, 2756.

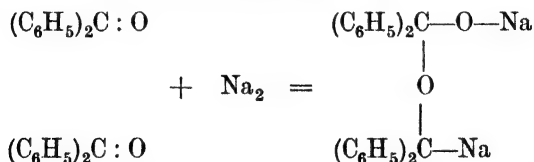
The facts described in the foregoing pages give some idea of the interesting points presented by these alkali-aryl derivatives ; and very little thought will show that they suggest some problems which will have to be taken into account in framing the ultimate theory of valency.

4. *The Metal-ketyls*

During an investigation of the action of sodium upon certain aldehydes and ketones dissolved in indifferent solvents, Beckmann and Paul [1] observed that diaryl ketones (such as benzophenone) yielded results which were surprising in more ways than one. In the first place, the reaction which occurred did not lead to any evolution of hydrogen ; secondly, the products were strongly coloured ; and, thirdly, they were extraordinarily sensitive materials with respect to oxygen or moisture.

The dark-blue product which was thus prepared from benzophenone had a composition corresponding to one molecule of the ketone combined with one atom of sodium.* When acted upon by water it yielded, according to the conditions, either a mixture of benzophenone and benzohydrol, $C_6H_5—CH(OH)—C_6H_5$, or else a mixture of these two products along with benzopinacoline, $(C_6H_5)_2C(OH)—(HO)C(C_6H_5)_2$. On treatment with carbon dioxide, a yellow powder was obtained which, when decomposed by water, gave benzophenone and sodium benzilate, $(C_6H_5)_2C(OH) . COONa$.

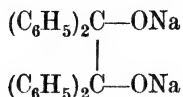
Beckmann and Paul assumed that the blue compound was formed according to the following equation :

$$\begin{matrix} (C_6H_5)_2C:O \\ \\ (C_6H_5)_2C:O \end{matrix} + Na_2 = \begin{matrix} (C_6H_5)_2C—O—Na \\ | \\ O \\ | \\ (C_6H_5)_2C—Na \end{matrix}$$

In view of the strangeness of these results, it is surprising that no further work was carried out in this field for a number of years ; but apparently the difficulties arising out of the great

[1] Beckmann and Paul, *Annalen*, 1891, **266**, 1.

* This result, of course, does not enable us to determine whether the material is composed of one molecule of ketone plus one atom of sodium or of two molecules of ketone united to two sodium atoms.

reactivity of the substances prevented the matter being examined, until in 1903, Acree [1] repeated the experiments. To account for the results, he proposed the following formula for the blue compound :

$$\begin{array}{c} (C_6H_5)_2C\text{—}ONa \\ | \\ (C_6H_5)_2C\text{—}ONa \end{array}$$

At first sight, this structure gives no reason for the marked colour of the compound, for according to all normal rules a sodium derivative of this description should be colourless.

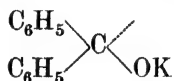
There the matter rested, however, until Schlenk and Weickel [2] approached the field with fresh ideas. In order to obtain a better crystalline material, they chose for their investigation not benzophenone, but di-diphenyl ketone, $(C_6H_5 . C_6H_4)_2C : O$.

Schlenk and Weickel attempted to determine the molecular weight of the sodium derivative in order to see whether its molecule contained one or two sodium atoms ; but in this they were unsuccessful, since according to them the coloured solutions contain colloidal or highly complex forms of the material, so that the results of ordinary molecular weight determinations are of no value. At a later date, Schlenk and Thal [3] surmounted this difficulty in a very ingenious manner. A solution of the ketone was placed in an air-free, nitrogen-filled boiling-point apparatus and the boiling-point was carefully determined. Pieces of pure metallic potassium were then added to the solution, and the boiling-point of the now coloured liquid was determined. No change in boiling-point was found, which, of course, proves that the same number of molecules is present in both cases. This excludes the possibility of the formation of compounds having formulae like those of Beckmann-Paul or Acree, since in those cases the number of molecules in solution would be lessened after the reaction, owing to two ketone molecules uniting to form a single molecule of the sodium derivative. Thus although the actual molecular weight of the solid sodium derivative remains unknown, the Schlenk-Thal experiments prove that the reaction initially consists in the union of one atom of alkali metal with one molecule of ketone.

[1] Acree, *Am. Chem. J.*, 1903, **29**, 604.
[2] Schlenk and Weickel, *Ber.*, 1911, **44**, 1182.
[3] Schlenk and Thal, *Ber.*, 1913, **46**, 2840.

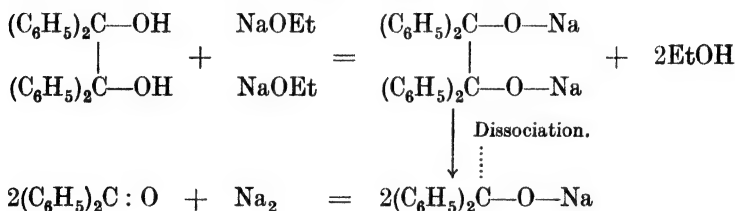
A further experiment of Schlenk and Thal served to clear up the whole matter, although at the first glance it seems rather to confuse the problem. When benzopinacone is suspended in benzene and treated with an alcoholic solution of sodium ethylate, the same sodium derivative is formed as is obtained by the action of sodium upon benzophenone. This appears to support the Acree formula; but the Acree formula will not agree with the boiling-point phenomena. How can these results all be brought into concord?

Schlenk and Thal suggested the simplest explanation by assuming that the coloured materials are really free radicles containing trivalent carbon atoms. On that assumption, the sodium derivative of benzophenone will have the formula

$$\begin{matrix} C_6H_5 \diagdown & & \diagup \\ & C & \\ C_6H_5 \diagup & & \diagdown OK \end{matrix}$$

and the production of this substance from benzopinacone and benzophenone can be expressed as shown below:

$$\begin{matrix} (C_6H_5)_2C\text{—}OH & & NaOEt & & (C_6H_5)_2C\text{—}O\text{—}Na & & \\ | & + & & = & | & + & 2EtOH \\ (C_6H_5)_2C\text{—}OH & & NaOEt & & (C_6H_5)_2C\text{—}O\text{—}Na & & \end{matrix}$$

$$\downarrow \text{ Dissociation.}$$

$$2(C_6H_5)_2C:O + Na_2 = 2(C_6H_5)_2C\text{—}O\text{—}Na$$

This explanation is now accepted * as the most probable solution of the problem; and these alkali derivatives of the diaryl ketones (and certain other substances to be mentioned later), which contain a trivalent carbon atom carrying the group —ONa in addition to two hydrocarbon radicles, are termed *metal-ketyls*.

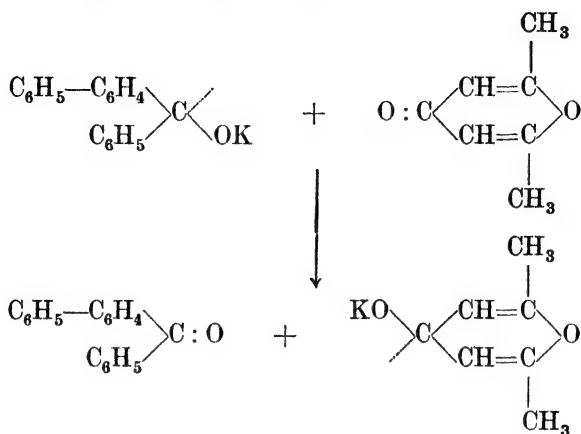
Although the direct action of sodium furnishes satisfactory yields of metal-ketyls from certain ketones, it gives poor results in other cases; and with these last compounds a different method is generally employed. The most soluble of all the known metal-ketyls is potassium phenyl-diphenyl ketyl, $C_6H_5 . C_6H_4\text{—}C(OK)\text{—}C_6H_5$. When an ethereal solution of this is mixed with dimethyl-pyrone, also dissolved in ether, a double

* Compare, however, Schmidlin, *Das Triphenylmethyl* (1914), pp. 186 ff.

decomposition occurs which yields phenyl-diphenyl ketone and the potassium ketyl of dimethyl-pyrone :

$$\begin{array}{c} C_6H_5\text{—}C_6H_4 \\ C_6H_5 \end{array}\!\!>\!\dot{C}\!\!<\!OK \;+\; O:C\!\!<\!\begin{array}{l} CH{=}C(CH_3) \\ CH{=}C(CH_3) \end{array}\!\!>\!O$$

$$\downarrow$$

$$\begin{array}{c} C_6H_5\text{—}C_6H_4 \\ C_6H_5 \end{array}\!\!>\!C:O \;+\; \begin{array}{c} KO \\ \end{array}\!\!>\!\dot{C}\!\!<\!\begin{array}{l} CH{=}C(CH_3) \\ CH{=}C(CH_3) \end{array}\!\!>\!O$$

The bright red potassium ketyl of dimethyl-pyrone is precipitated, leaving the solution colourless.

A large number of potassium ketyls have been prepared by either of the foregoing methods ; and it may be convenient to gather them together in a table. The first column gives the name of the ketone from which the ketyl was prepared ; in the second column, the composition of the ketyl is placed ; whilst the third column contains notes of the ketyls' tints.

Ketone.	*Ketyl.*	*Colour.*
Dimethyl-pyrone . .	$C_7H_8O_2K$	Bright cinnabar-red
β-Benzopinacoline . .	$C_{26}H_{20}OK$	Deep red
Phthalophenone . .	$C_{20}H_{14}OK$	Dark red
N-Methyl-isatin . .	$C_9H_7O_2K$	Deep blue
O-Methyl-isatin . .	$C_9H_7O_2K$	Deep violet
m-Dibenzoyl-benzene .	$C_{20}H_{14}O_2K$	Dark red
p-Dibenzoyl-benzene .	$C_{20}H_{14}O_2K_2$ *	Deep red
Furil	$C_{10}H_6O_4K$	Black
Phenanthrenequinone .	$C_{14}H_8O_2K$	Dark brown

In addition to the simple ketyls given in the table above, some others remain to be described, since their composition

* This dipotassium derivative might be regarded as having either a normal quinonoid structure or as possessing two trivalent carbon atoms in the *para*-position with regard to each other. In view of the fact that it ignites spontaneously when exposed to air, the latter formulation seems the more probable of the two.

has some complexity. From chromone, a compound is obtained which appears to contain one molecule of the ketyl $C_9H_6O_2K$ combined with one molecule of chromone itself, $C_9H_6O_2$. Somewhat similar results were obtained with *p*-benzoquinone. In one case a compound was obtained which had the composition corresponding to one molecule of ketyl plus one molecule of quinone, ($C_6H_4O_2K + C_6H_4O_2$). The results varied so much from experiment to experiment, however, that too much reliance need not be placed on this. It appears possible that something akin to quinhydrone formation may be taking place in these cases.

The behaviour of *o*-benzoquinone is peculiar. On treating an ethereal solution of potassium phenyl-diphenyl ketyl with this quinone a dark-green precipitate is formed, which later changes to a white material. On examination, this last substance is found to be the potassium derivative of catechol. If the method be reversed, so that the ketyl is added to the quinone—thus avoiding the presence of an excess of potassium—the solution turns intensely red-violet in tint. This phenomenon has not yet been completely cleared up, owing to the difficulty of isolating the extremely unstable substances involved.

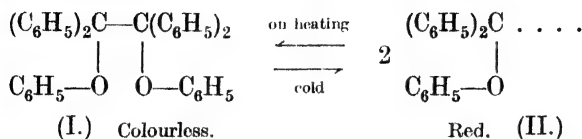
Before leaving this section of the subject, mention must be made of one or two other investigations in an allied field. By the action of potassium upon benzil in dry benzene solution with the usual precautions, Staudinger and Binkert [1] obtained two products. With one molecule of potassium, a deep blue-violet solution was produced; whilst the addition of a second molecule of potassium yielded a deep-red solution from which a dark-red precipitate was thrown down. The action of oxygen on the precipitate produced mainly potassium benzoate with 20–30 per cent. of benzilic acid. It was suggested that the precipitate was the potassium derivative of dihydroxy-stilbene, $KO—C(C_6H_5):(C_6H_5)C—OK$; and that the substance containing half the quantity of potassium was a quinhydrone type.

Wieland [2] has prepared a compound which appears to be a phenyl ether corresponding in type to the metal-ketyls. When

[1] Staudinger and Binkert, *Helv. Chim. Acta*, 1922, **5**, 703; Scheuing and Hensle, *Annalen*, 1924, **440**, 172.

[2] Wieland, *Ber.*, 1911, **44**, 2550.

triphenylmethyl peroxide $(C_6H_5)_3C—O—O—C(C_6H_5)_3$, is dissolved in hot naphthalene it is dissociated into the two free radicles $(C_6H_5)_3C—O$. These undergo rearrangement in part into the form $(C_6H_5)_2C—O—C_6H_5$; and by the union of these two, the compound (I.) shown below is produced :

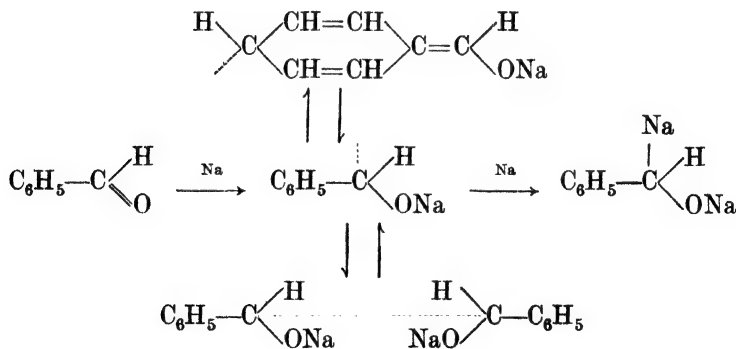
$$\underset{\text{(I.) Colourless.}}{\begin{array}{cc}(C_6H_5)_2C & —C(C_6H_5)_2 \\ | & | \\ C_6H_5—O & O—C_6H_5\end{array}} \underset{\text{cold}}{\overset{\text{on heating}}{\rightleftharpoons}} 2\ \underset{\text{Red. (II.)}}{\begin{array}{c}(C_6H_5)_2C \cdots\cdot \\ | \\ C_6H_5—O\end{array}}$$

The present point of interest in the matter is that the solution in hot naphthalene is red in colour, which may reasonably be ascribed to the presence of the trivalent carbon derivative (II.) by dissociation, as indicated in the foregoing formulae.

Benzaldehyde and the ethyl and phenyl esters of benzoic acid have been found to react with sodium, yielding highly-coloured reactive materials.[1] In order to account for the properties of the mono- and disodium derivatives of benzaldehyde, Blicke has put forward the following scheme, which brings the materials into parallel with compounds of the triphenylmethyl series :

$$\begin{array}{c}\begin{array}{l}H \\ \diagup\end{array}\!>\!C\!<\!\begin{array}{l}CH{=}CH \\ CH{=}CH\end{array}\!>\!C{=}C\!<\!\begin{array}{l}H \\ ONa\end{array} \\ \upharpoonleft\downharpoonright\end{array}$$

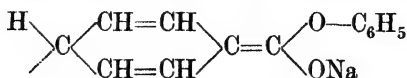
$$C_6H_5—C\!\begin{array}{l}\diagup H \\ \diagdown O\end{array} \xrightarrow{Na} C_6H_5—C\!\begin{array}{l}\diagup H \\ \diagdown ONa\end{array} \xrightarrow{Na} C_6H_5—\overset{Na}{\overset{|}{C}}\!\begin{array}{l}\diagup H \\ \diagdown ONa\end{array}$$

$$\downharpoonleft\upharpoonright$$

$$C_6H_5—C\!\begin{array}{l}\diagup H \\ \diagdown ONa\end{array} \cdots\cdots \begin{array}{r}H \diagdown \\ NaO \diagup\end{array}\!C—C_6H_5$$

A somewhat similar series of changes is assumed to account for

[1] Church, *Annalen*, 1863, **128**, 295; Frey, *Ber.*, 1895, **28**, 2520; Wahl. *Compt. rend.*, 1908, **147**, 73; Scheibler and others, *Ber.*, 1920, **53**, 390 ff.; *Annalen*, 1923, **434**, 268; Lachman, *J. Amer. Chem. Soc.*, 1923, **45**, 708; Blicke, *ibid.*, 1924, **46**, 2560; 1925, **47**, 229.

the action of sodium upon phenyl benzoate, the quinonoid material in this case being regarded as having the structure :

$$\begin{matrix} H \\ \end{matrix}\!\!\!>C<\!\!\begin{matrix} CH=CH \\ CH=CH \end{matrix}\!\!>C=C<\!\!\begin{matrix} O-C_6H_5 \\ ONa \end{matrix}$$

It can be seen from the above formulae that Blicke assumes the trivalency of one of the benzenoid carbon atoms, whereas Schlenk postulated trivalency in an extra-cyclic carbon atom.

Some account must now be given of the reactions of these interesting materials.[1] It must be remembered that, just like the alkali-alkyls and alkali-aryls, the metal-ketyls must be handled entirely in a nitrogen atmosphere, since the least trace of air or moisture would lead to their decomposition. In order to simplify the formulae, we shall replace the symbol $C_6H_5—C_6H_4—$ by —R, so that $(C_6H_5 . C_6H_4)_2CO$ becomes R_2CO.

When the sodium derivative of di-diphenyl-ketone is dissolved in ether, it yields a deep-green solution. Admission of oxygen leads to an immediate decolorization and a voluminous precipitate is deposited, which on examination is found to be a mixture of sodium peroxide with the original ketone. This agrees well with Schlenk's hypothesis as to the constitution of the ketyls.

Iodine reacts with the metal-ketyls, yielding an alkali iodide and regenerating the original ketone.

The action of methyl iodide is rather peculiar. When it is added to an ethereal solution of sodium di-diphenyl ketyl, the green solution changes its colour to yellow ; and a precipitation of sodium iodide and the original ketone takes place. If the ethereal solution be now shaken with water, it goes colourless. On separating off the water and evaporating the ethereal solution, a residue is obtained which proves to be di-diphenyl-methyl carbinol, $R_2C(CH_3) . OH$.

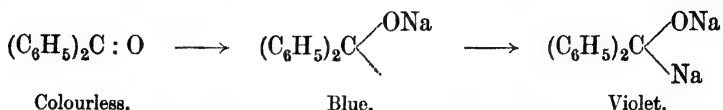
With water, the sodium derivative of di-diphenyl ketone yields di-diphenyl carbinol, $R_2CH . OH$, and the original ketone. Nothing corresponding to a pinacone was detected.

Like the alkali-triaryls, the metal-ketyls have the power of combining with an atom of sodium by utilizing their free

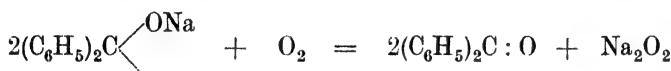
[1] Schlenk and Weickel, *Ber.*, 1911, **44**, 1182; Schlenk and Thal, *Ber.*, 1913, **46**, 2840.

valency.[1] When excess of sodium powder is added to an ethereal solution of benzophenone, the deep blue colour of the mono-sodium derivative is first produced; but on standing, it changes to a dark-violet * tint:

$$(C_6H_5)_2C:O \longrightarrow (C_6H_5)_2C\langle^{ONa}_{\cdot} \longrightarrow (C_6H_5)_2C\langle^{ONa}_{Na}$$

Colourless. Blue. Violet.

These disodium derivatives are, like the mono-sodium compounds, extremely sensitive to the action of oxygen or moisture. Oxygen converts them first into metal-ketyls; and finally the original ketone is regenerated:

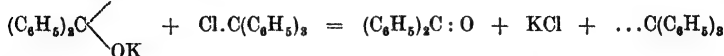
$$2(C_6H_5)_2C\langle^{ONa}_{Na} + O_2 = 2(C_6H_5)_2C\langle^{ONa}_{\cdot} + Na_2O_2$$

$$2(C_6H_5)_2C\langle^{ONa}_{\cdot} + O_2 = 2(C_6H_5)_2C:O + Na_2O_2$$

Water decomposes them smoothly with the formation of secondary alcohols:

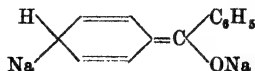
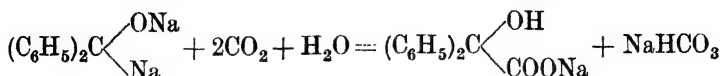
$$(C_6H_5)_2C\langle^{ONa}_{Na} + 2H_2O = (C_6H_5)_2CH.OH + 2NaOH$$

Carbon dioxide decomposes the disodium derivatives with the production of acids of the benzilic series:

[1] Schlenk, *Houben-Weyl's Methoden der organischen Chemie*, Vol. IV., p. 977; Schlenk and others, *Ber.*, 1914, **47**, 486. When a metal-ketyl is treated with triphenyl-chloro-methane, triphenylmethyl is formed, and the original ketone is regenerated:

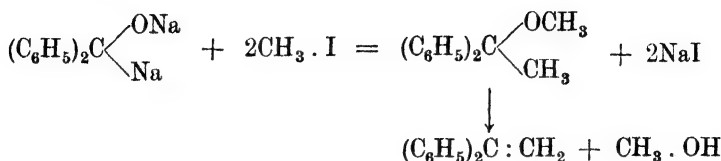
$$(C_6H_5)_2C\langle^{\cdot}_{OK} + Cl.C(C_6H_5)_3 = (C_6H_5)_2C:O + KCl + \ldots C(C_6H_5)_3$$

* Compare the similar colour-changes in the formation of the mono- and di-sodium derivatives of anthracene (p. 275). The coloration of $(C_6H_5)_2C(ONa)Na$ seems difficult to explain on ordinary assumptions. It would certainly be more easily accounted for by a formula such as

$$\begin{matrix}H \\ Na\end{matrix}\rangle C_6H_4\langle = C\langle\begin{matrix}C_6H_5 \\ ONa\end{matrix}$$

$$(C_6H_5)_2C\begin{cases}ONa\\Na\end{cases} + 2CO_2 + H_2O = (C_6H_5)_2C\begin{cases}OH\\COONa\end{cases} + NaHCO_3$$

The action of alkyl halides is peculiar. Labile ethers of tertiary alcohols are formed first, which then decompose readily to yield ethylenic derivatives:

$$(C_6H_5)_2C\begin{cases}ONa\\Na\end{cases} + 2CH_3 . I = (C_6H_5)_2C\begin{cases}OCH_3\\CH_3\end{cases} + 2NaI$$

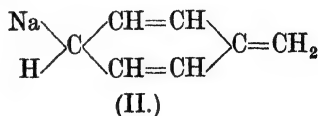
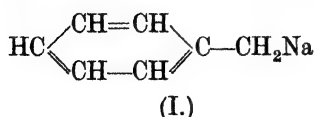
$$\downarrow$$

$$(C_6H_5)_2C : CH_2 + CH_3 . OH$$

5. *Conclusion*

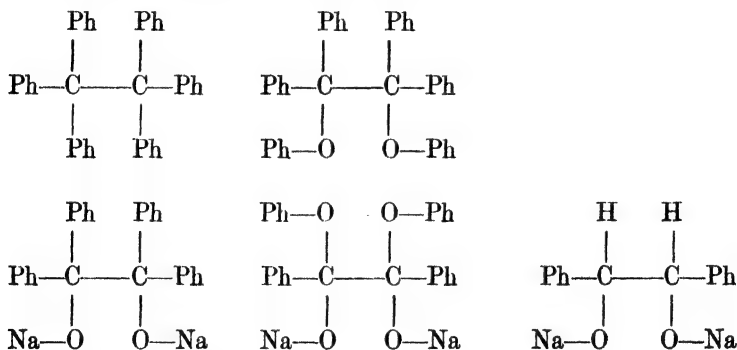
The facts described in earlier sections of this chapter suggest a number of problems which will doubtless be cleared up in due course by further investigation.

It is perhaps too early as yet to come to any definite conclusion with regard to the structure of the metal-ketyls; but the evidence at present available seems to favour Blicke's views rather than Schlenk's. In the first place, lithium phenyl is colourless; which proves that the mere direct linking of an alkali atom to carbon does not produce colour, even when a phenyl nucleus is present in the molecule. In marked distinction to this we have sodium benzyl, which is a strongly coloured compound. Since colour in the benzene series is generally associated with a quinoid structure, it is hard to see why a substance of the type (I.) should be coloured at all; but if intramolecular rearrangement be assumed, then, with the structure (II.), the sodium derivative would be markedly tinted:

$$HC\begin{cases}CH{=}CH\\CH{-}CH\end{cases}C{-}CH_2Na \qquad \begin{matrix}Na\\H\end{matrix}{>}C\begin{cases}CH{=}CH\\CH{=}CH\end{cases}C{=}CH_2$$

(I.) (II.)

This formula for sodium benzyl, it will be noted, involves no trivalency of carbon and therefore leaves the parallelism with the simpler metal alkyls in existence The colourlessness of lithium phenyl would be accounted for by the fact that no such quinonoid structure can be composed for it.

If this structure (II.) be accepted for sodium benzyl, however, it seems possible—on the analogy with triphenylmethyl—that in some of its reactions sodium benzyl should give rise to a hydrocarbon with the structure $C_6H_5 . CH_2 . C_6H_4 . CH_3$, which would be a parallel to the Ullmann and Borsum hydrocarbon $(C_6H_5)_3C . C_6H_4 . CH(C_6H_5)_2$, which is formed in certain conditions from triphenylmethyl. Further experiment will probably settle this question.

The increase in the number of substances containing trivalent carbon atoms offers some prospect of discovering the conditions which govern the dissociation of carbon compounds by the rupture of single bonds and the formation of free radicles.[1] At the present time it is known that substances of the following types can be split apart at the central bond. For the sake of simplicity the phenyl group may be printed as Ph.

Examination of these formulae seems to dispose of the older idea that the production of a trivalent carbon atom necessitated a large accumulation of highly unsaturated groups on that atom; for the trivalent atom in C_6H_5—CH(ONa)— is certainly not overloaded with centres of residual affinity. It will be of considerable interest to see how further research in this field will develop; for it bids fair to give us some clearer ideas about the whole problem of abnormal valency.

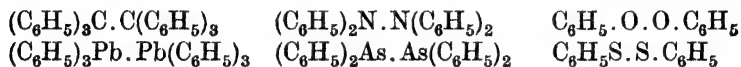
[1] Compare Kraus, *J. Amer. Chem. Soc.*, 1924, **46**, 2196.

CHAPTER XIV

OTHER CASES OF ABNORMAL VALENCY

A.—INTRODUCTORY

IN view of the interest excited by the triphenylmethyl problem from 1900 onwards, it seems strange that no one at that time appears to have though of examining other compounds which show some structural analogy with hexaphenyl-ethane.

$(C_6H_5)_3C.C(C_6H_5)_3$	$(C_6H_5)_2N.N(C_6H_5)_2$	$C_6H_5.O.O.C_6H_5$
$(C_6H_5)_3Pb.Pb(C_6H_5)_3$	$(C_6H_5)_2As.As(C_6H_5)_2$	$C_6H_5S.S.C_6H_5$

In each of the formulae shown above there is a symmetrical structure; all the formulae contain a central single bond in the molecule; and the various substances represent the highest possible phenyl-substitution product of their type.

Tetraphenylhydrazine was already known at the time when triphenylmethyl was arousing interest by its peculiar nature; yet no one seems to have been struck by the analogy between it and hexaphenyl-ethane; and it was quite accidentally, in 1906, that the close correspondence between the two series was first brought out in practice. It has since been shown that, just as the free radicle triphenylmethyl can exist in solution, so can the corresponding diphenylhydrazyl grouping $(C_6H_5)_2N$ appear in the free state; and if carbon is to be considered as a trivalent element in certain circumstances, we cannot deny the possibility of divalent nitrogen derivatives. Between the two series a strong resemblance undoubtedly exists, though the bond N—N is much less readily ruptured than the single linkage between the central carbon atoms of Gomberg's hydrocarbon.

With regard to the analogous phenyl derivatives of the divalent elements, it is found that experimental evidence points to the possibility of aryl peroxides yielding dissociation products;[1] whilst apparently diphenyl disulphide can, under

[1] Pummerer and Cherbuliez, *Ber.*, 1914, 47, 2957.

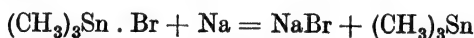
certain circumstances, give rise to a free radicle. There are indications that derivatives of monovalent mercury may be capable of existence. In the following sections of this chapter the behaviour of these compounds will be briefly surveyed.

B.—Trivalent Tin

In its organic compounds, tin shows a kinship with both zinc and carbon. A polymeric form of tin dimethyl has been obtained,[1] which is spontaneously inflammable in air, like zinc dimethyl. On the other hand, alkyl derivatives of quadrivalent tin have been known for some time; and the optical activity of asymmetric tin compounds furnishes a parallel to the case of the optically active carbon derivatives. These cases, however, do not go outside our normal ideas of the valency of tin, since the compounds might be regarded as being derived from $SnCl_2$ or $SnCl_4$.

The case of trimethyl-tin,[2] however, shows the metallic atom in possession of a valency different from that manifested in the chlorides or hydrides; and apparently we have here to deal with another example of abnormal valency.

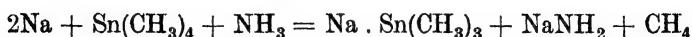
The free trimethyl-tin group $(CH_3)_3Sn$, is quantitatively obtained by the reduction of trimethyl-tin halides with metallic sodium in liquid ammonia solution:

$$(CH_3)_3Sn . Br + Na = NaBr + (CH_3)_3Sn$$

Trimethyl-tin is a white solid melting at 23° C. It boils in an inert atmosphere at 182° C., with some decomposition. When distilled in air, its vapour flashes, owing to combination with oxygen. In boiling benzene, the molecular weight of trimethyl-tin at low concentrations is 171, whilst at high concentrations it is 352. As the calculated value for $(CH_3)_3Sn$ is 164, this suggests that in concentrated solution the material is present as $(CH_3)_3Sn—Sn(CH_3)_3$ and dissociates into trimethyl-tin as the solution is diluted.

[1] Kraus and Greer, *J. Amer. Chem. Soc.*, 1925, **47**, 2568.

[2] Rügheimer, *Annalen*, 1910, **364**, 5; Kraus, *Rec. trav. chim.*, 1923, **42**, 588; *J. Amer. Chem. Soc.*, 1924, **46**, 2196; Kraus and Callis, *ibid.*, 1923, **45**, 2624; Kraus and Greer, *ibid.*, 1923, **45**, 3078; Kraus and Sessions, *ibid.*, 1925, **47**, 2361.

In liquid ammonia solution, trimethyl-tin combines directly with sodium, yielding sodium trimethyl-tin, $Na . Sn(CH_3)_3$, which is also obtainable by the action of sodium upon tetramethyl-tin in liquid ammonia :

$$2Na + Sn(CH_3)_4 + NH_3 = Na . Sn(CH_3)_3 + NaNH_2 + CH_4$$

This sodium derivative combines with oxygen to form $[(CH_3)_3Sn]_2O$ and with sulphur to yield the corresponding sulphide. By acting on the sodium derivative with a triethyl-tin halide, the compound $(CH_3)_3Sn—Sn(C_2H_5)_3$ has been prepared. With chlorine, trimethyl-tin gives trimethyl stannonium chloride, $(CH_3)_3Sn . Cl$.

The trimethyl-tin radicle is of considerable interest, since in its case all possible complexities of constitution due to the presence of phenyl nuclei are excluded and the dissociation indicated by the molecular weight determinations is evidently a simple one.

C.—Trivalent Lead

When to an ethereal solution of magnesium *p*-2-xylyl bromide, finely-powdered lead dichloride is added in the proportion required by the equation :

$$3PbCl_2+6Br.Mg.C_8H_9=2Pb(C_8H_9)_3+Pb + 3MgCl_2 + 3MgBr_2$$

a greenish-yellow crystalline material can be isolated from the reaction-mixture.[1] The molecular weight of the substance, determined by the cryoscopic method in benzene solution, corresponds to the formula $(C_8H_9)_3Pb . Pb(C_8H_9)_3$; and the body appears to be the lead analogue of hexaphenyl-ethane.

It does not oxidize in air under ordinary conditions, wherein it differs from its carbon analogue ; but with bromine it yields $Br . Pb(C_8H_9)_3$, just as triphenylmethyl gives triphenyl-bromomethane.

The lead derivative is quite stable up to a temperature of 220° ; but in solution it appears to be remarkably photosensitive, being readily decomposed by the action of light. By the Grignard reaction, it yields lead tetra-*p*-2-xylyl, which is only decomposed at temperatures above 270°.

[1] Krause and Schmitz, *Ber.*, 1919, 52 [B], 2165.

Attempts to prepare the corresponding simpler derivatives (such as lead triphenyl) by the same method were not successful, the tetra-aryl compounds being obtained instead.

D.—Divalent and Quadrivalent Nitrogen

1. *The Tetra-aryl-hydrazines*

Tetraphenyl-hydrazine can be prepared either by the action of iodine upon the sodium derivative of diphenylamine [1] or by the oxidation of diphenylamine in an organic solvent by means of lead oxide or potassium permanganate.[2] Obtained by any of these methods, it is a colourless solid melting at 144° C.

As a class the tetra-aryl-hydrazines are stable substances when in the solid state, though they are easily affected by light and are rapidly changed when dissolved in various solvents. Nascent hydrogen converts them with ease into two molecules of the diarylamine from which they were originally produced.

Their most peculiar behaviour is observed when they are treated with acid. In their ordinary form they possess no basic properties; for anhydrous mineral acids give no normal (colourless) salts. On the other hand, when they are acted on by acids, even in organic solvents, they exhibit intense colours,* green, blue, or violet.[2] The coloured derivatives can be isolated in an impure condition; and when they are treated with alkali they regenerate the parent hydrazines. They must therefore be regarded as salt-like addition products of the undecomposed hydrazines.[3]

These coloured products are extremely labile and soon decompose under ordinary conditions, yielding a mixture of several different compounds.[4] Thus in presence of acids, tetraphenyl-hydrazine gives diphenylamine, *p*-chloro-anilido-triphenylamine

[1] Chattaway and Ingle, *J.*, 1895, **67**, 1090.

* Similar colours are obtained with halogens, thionyl chloride, ferric chloride, aluminium chloride, zinc chloride, and the pentachlorides of phosphorus and antimony.

[2] Wieland and Gambarjan, *Ber.*, 1906, **39**, 1499.

[3] Wieland, *Die Hydrazine*, 1913, p. 63.

[4] Wieland, *Annalen*, 1911, **381**, 200; 1912, **393**, 169; *Ber.*, 1907, **40**, 4262; 1908, **41**, 3478.

(I.), diphenylbenzidine (II.), and a perazine-derivative (III.):

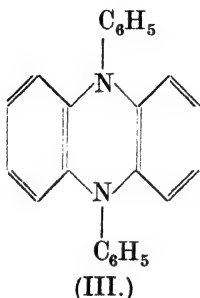
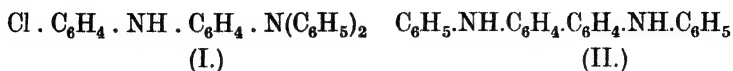
$Cl . C_6H_4 . NH . C_6H_4 . N(C_6H_5)_2$ (I.) $C_6H_5.NH.C_6H_4.C_6H_4.NH.C_6H_5$ (II.)

C_6H_5

N

N

C_6H_5

(III.)

The presence of acids is not essential to ensure the breakdown of the tetra-aryl-hydrazines; for with some of them it is only necessary to heat the substance itself in benzene or toluene solution, whereupon decomposition takes place and follows a course similar to that traced when acids are present, though naturally, with slight variations due to the absence of acidic radicles.[1]

The influence of solvents upon the hydrazines manifests itself in another manner. As has been mentioned, the hydrazines are colourless in the solid state; but when they are dissolved in organic solvents and then heated, a marked colour makes its appearance,* which disappears again if the substance be cooled immediately. Colours also make their appearance when the hydrazines are bombarded with cathode rays and kept cool with liquid air.[2] As soon as the bombardment ceases, the substance reverts to its original colourless condition.†

When treated with nitrogen peroxide in toluene solution at 90° C., tetraphenyl-hydrazine reacts and produces

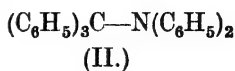
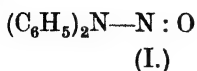
[1] Wieland and Lecher, *Ber.*, 1912, **45**, 2600.

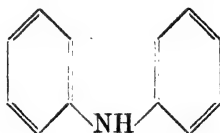
* Cryoscopic molecular weight determinations prove that the substance $[(CH_3)_2N . C_6H_4]_2N . N[C_6H_4N(CH_3)_2]_2$ is dissociated to an extent of 10 per cent. in benzene solution and 21 per cent. in a solution of nitrobenzene (Wieland, *Ber.*, 1915, **48**, 1078).

[2] Wieland, *Annalen*, 1911, **381**, 200.

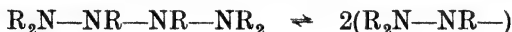
† Exactly similar results are obtained with triphenylmethyl derivatives (Schlenk and Herzenstein, *Annalen*, 1910, **372**, 1).

nitrosodiphenylamine (I.); whilst with triphenylmethyl it yields triphenylmethyl-diphenylamine * (II.):

$$(C_6H_5)_2N—N:O \qquad (C_6H_5)_3C—N(C_6H_5)_2$$
$$\text{(I.)} \qquad\qquad\qquad \text{(II.)}$$

Alkali metals act on the tetra-aryl-hydrazine with greater or less readiness, producing compounds of the type $R_2:N.Na$, the reaction being similar to that observed in the case of triphenylmethyl.[1]

In conclusion, it must be pointed out that in one case at least the general synthetic method for preparing tetra-aryl hydrazines breaks down. When carbazole—

is oxidized with the usual reagents, it does not behave like diphenylamine,[2] though it contains the diphenylamine skeleton. Apparently the presence of the pyrrol ring in the compound has some influence upon the reaction; and it is suggested that the extra valency of the nitrogen atom is in this case absorbed by that portion of the molecule.

Results somewhat similar to those in the tetra-aryl-hydrazines have been obtained by Goldschmidt [3] in the series of hexa-substituted tetrazanes, which appear to dissociate thus:

$$R_2N—NR—NR—NR_2 \rightleftharpoons 2(R_2N—NR—)$$

2. *Wieland's Hypothesis of Divalent Nitrogen*

In order to explain the reactions described in the foregoing section, Wieland [4] proposes to regard the tetra-aryl-hydrazines as analogues of the triphenylmethyl series; so that under certain

* Exactly similar results were obtained with triphenylmethyl derivatives (Schlenk and Herzenstein, *Annalen*, 1910, **372**, 1).

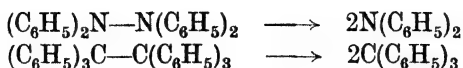
[1] Schlenk and Marcus, *Ber.*, 1914, **47**, 1664.

[2] Wieland and Gambarjan, *Ber.*, 1906, **39**, 1499.

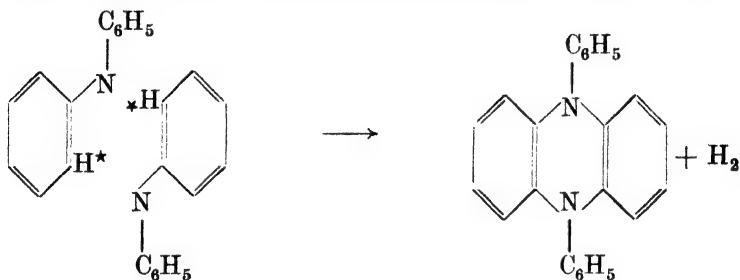
[3] Goldschmidt, *Annalen*, 1924, **437**, 194.

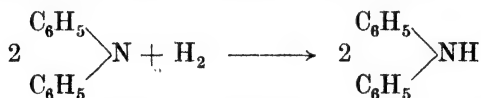
[4] Wieland, *Annalen*, 1911, **381**, 200; 1912, **392**, 127; 1913, **401**, 233.

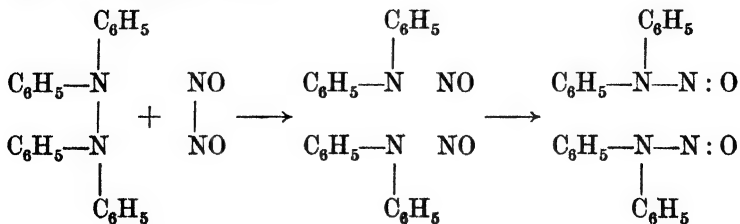
conditions he assumes a depolymerization of the substituted hydrazine which parallels the formation of triphenylmethyl from hexaphenyl-ethane :

$$(C_6H_5)_2N{-}N(C_6H_5)_2 \longrightarrow 2N(C_6H_5)_2$$
$$(C_6H_5)_3C{-}C(C_6H_5)_3 \longrightarrow 2C(C_6H_5)_3$$

The colours observed when tetraphenyl-hydrazine derivatives are treated with acids or with reagents such as stannic chloride and thus brought into line with those which are obtained in the triphenylcarbinol series under similar conditions.

The formation of a dihydrophenazine derivative and diphenylamine is explained by the mutual oxidation and reduction of four free radicles in the following manner. In the first place, two of them unite with the elimination of two hydrogen atoms (marked with an asterisk), to form diphenyl-dihydrophenazine :

$$2\,C_6H_4(H^*){-}N{-}C_6H_5 \longrightarrow C_6H_4{<}\begin{matrix}N(C_6H_5)\\N(C_6H_5)\end{matrix}{>}C_6H_4 + H_2$$

These two hydrogen atoms, thus set free, then reduce the two other free radicles to form two molecules of diphenylamine :

$$2\,\begin{matrix}C_6H_5\\C_6H_5\end{matrix}{>}N + H_2 \longrightarrow 2\,\begin{matrix}C_6H_5\\C_6H_5\end{matrix}{>}NH$$

The production of nitroso-diphenylamine, on this hypothesis, may be represented thus :

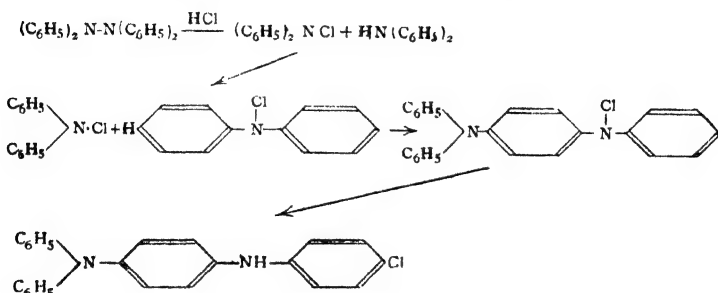
$$\begin{matrix}C_6H_5{-}N{-}C_6H_5\\ |\\ C_6H_5{-}N{-}C_6H_5\end{matrix} + \begin{matrix}NO\\ |\\ NO\end{matrix} \longrightarrow \begin{matrix}(C_6H_5)_2N & NO\\ (C_6H_5)_2N & NO\end{matrix} \longrightarrow \begin{matrix}(C_6H_5)_2N{-}N:O\\ (C_6H_5)_2N{-}N:O\end{matrix}$$

and the reaction with triphenylmethyl is simply a union of the two free radicles to form triphenylmethyl-diphenylamine :

$$(C_6H_5)_3C + N(C_6H_5)_2 \longrightarrow (C_6H_5)_3C—N(C_6H_5)_2$$

To account for the formation of *p*-chloro-anilido-triphenylamine, Wieland assumes that the first action of acids upon tetraphenyl-hydrazine is to decompose it into one molecule of diphenylamine and one molecule of chloro-diphenylamine, two molecules of which then interact as shown below :

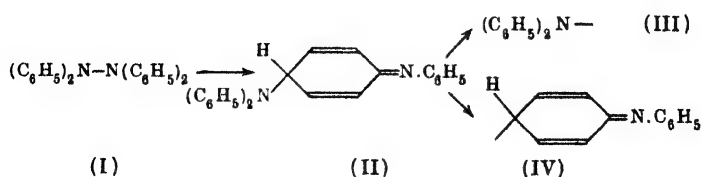
$$(C_6H_5)_2N\text{-}N(C_6H_5)_2 \xrightarrow{HCl} (C_6H_5)_2NCl + HN(C_6H_5)_2$$

$$(C_6H_5)_2N\cdot Cl + H\text{-}C_6H_4\text{-}N(Cl)\text{-}C_6H_5 \rightarrow (C_6H_5)_2N\text{-}C_6H_4\text{-}N(Cl)\text{-}C_6H_5$$

$$\rightarrow (C_6H_5)_2N\text{-}C_6H_4\text{-}NH\text{-}C_6H_4\text{-}Cl$$

3. *An Application of the Quinonoid Hypothesis*

The parallelism between the tetraphenyl-hydrazine derivatives and the triphenylmethyl group is so close that it seems not unwarrantable to extend to the former the ideas which have been used to account for the behaviour of the trivalent carbon compounds.

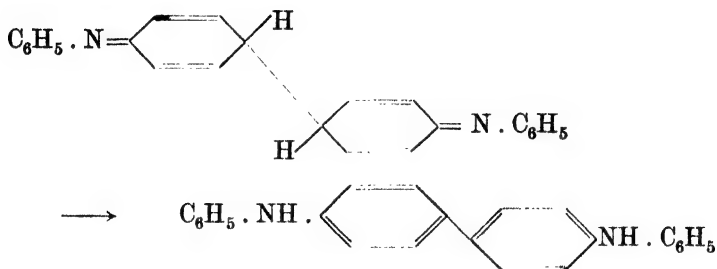
In the triphenylmethyl group, it was assumed that hexaphenyl-ethane was capable of intramolecular change resulting in a quinonoid structure. An analogous change in tetraphenylhydrazine would result in the formation of a compound of the type (II.) which, if we follow out the parallel, would dissociate into a benzenoid portion (III.) and a quinonoid part (IV.) :

$$\underset{(I)}{(C_6H_5)_2N—N(C_6H_5)_2} \longrightarrow \underset{(II)}{(C_6H_5)_2N(H)C_6H_4{=}N.C_6H_5} \rightarrow \underset{(III)}{(C_6H_5)_2N—} + \underset{(IV)}{(H)C_6H_4{=}N.C_6H_5}$$

The presence of the quinonoid structure here would account for the appearance of colour when colourless tetraphenylhydrazine is heated in solution, and also for the readiness with which the substance is affected by light.

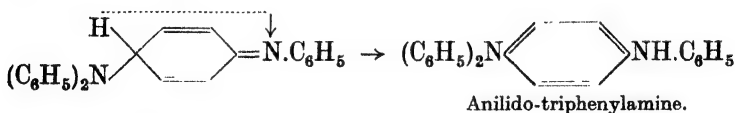
To account for the production of diphenylbenzidine from the hydrazine, it is only necessary to assume that two molecules of (IV.) join together and then rearrange themselves into the benzenoid form—

$C_6H_5 . N=C_6H_4<H$

$H>C_6H_4=N . C_6H_5$

$\longrightarrow \quad C_6H_5 . NH . C_6H_4-C_6H_4 . NH . C_6H_5$

To explain the production of *p*-chloro-anilido-triphenylamine it may be assumed that in acid solution the radicle $(C_6H_5)_2N$ is attacked by a chlorine ion, giving chloro-diphenylamine, after which the reactions would take place according to Wieland's suggestion. The occurrence of the parent substance, anilido-triphenylamine, which is noticed when tetraphenyl-hydrazine is heated in benzene solution, can be even more simply explained by a wandering of a hydrogen atom; thus recalling the formation of Ullmann and Borsum's hydrocarbon in the case of triphenylmethyl:

$$\begin{matrix}H \\ (C_6H_5)_2N\end{matrix}>C_6H_4=N.C_6H_5 \rightarrow (C_6H_5)_2N<C_6H_4>NH.C_6H_5$$

Anilido-triphenylamine.

The interaction with triphenylmethyl and with nitrogen peroxide is easily accounted for by assuming that these two reagents combine directly with the free benzenoid radicles (III.).

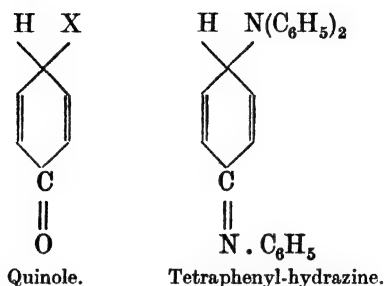
In order to make clear the formation of the perazine derivative it must be pointed out that along with one molecule of this substance, the reaction gives rise simultaneously to two molecules of diphenylamine. Now an examination of the quinonoid

structure proposed for tetraphenyl-hydrazine suggests a resemblance to the quinole constitution :

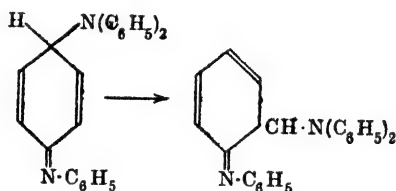
H X   H $N(C_6H_5)_2$

C   C

O $N . C_6H_5$

Quinole.   Tetraphenyl-hydrazine.

and just as some quinoles exhibit a wandering of the group X to the nucleus, so we may assume a similar wandering to take place in tetraphenyl-hydrazine, giving rise to a compound of the following structure :

H $N(C_6H_5)_2$ ⟶ $CH{\cdot}N(C_6H_5)_2$

$N{\cdot}C_6H_5$ $N{\cdot}C_6H_5$

Two molecules of this would combine directly to produce a perazine and at the same time eliminate two molecules of diphenylamine (as shown by the dotted line) for each molecule of perazine produced :

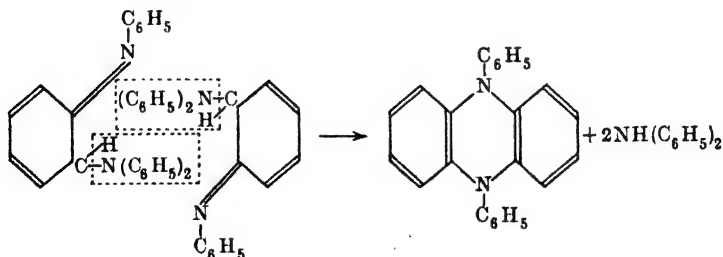
C_6H_5 C_6H_5

N   N

$(C_6H_5)_2N{-}C$, H

H, $C{-}N(C_6H_5)_2$ ⟶ $+ 2NH(C_6H_5)_2$

N   N

C_6H_5 C_6H_5

Thus in order to account satisfactorily for the various reactions of tetraphenyl-hydrazine, it is necessary to assume the following series of equilibria :—

$(C_6H_5)_2N-N(C_6H_5)_2$

$\rightleftharpoons$

$(C_6H_5)_2N$ H =N.C_6H_5

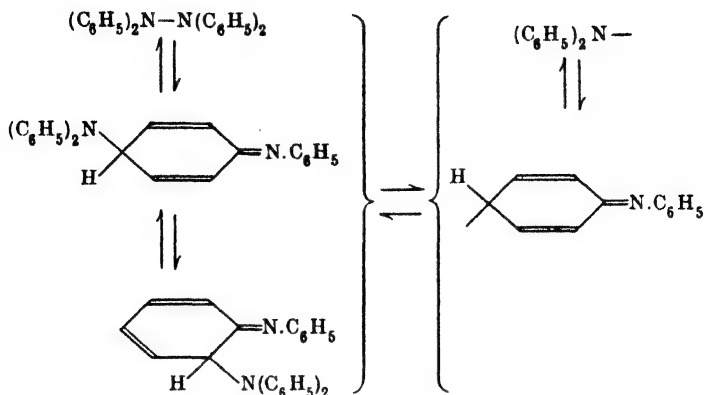
$\rightleftharpoons$

=N.C_6H_5 H $N(C_6H_5)_2$

$\rightleftharpoons$

$(C_6H_5)_2N-$

$\rightleftharpoons$

H =N.C_6H_5

4. *The Hexa-aryl-tetrazanes*

Goldschmidt [1] studied the oxidation of tri-aryl-hydrazines and detected the formation of tri-aryl-tetrazyls of the type $R_2N—NR—$, in which one of the nitrogen atoms is divalent.

When triphenyl-hydrazine, $(C_6N_5)_2N$. NH . C_6H_5, is oxidized in methyl ether solution with lead oxide at —60° C., the solution turns deep blue, and an almost colourless set of crystals is obtained which were shown to be hexaphenyl-tetrazane: $(C_6H_5)_2N.N(C_6H_5).(C_6H_5)N.N(C_6H_5)_2$. On redissolving the crystals, a blue solution is obtained which contains the free radicle triphenyl-hydrazyl; but after standing for a time, the colour alters to reddish-brown owing to the formation of diphenylamine and quinone-anil-phenyl-hydrazone.

The presence of a derivative of divalent nitrogen is proved by the following facts. Nitric oxide acts on the solution, yielding N-nitroso-triphenyl-hydrazine, $(C_6H_5)_2N.N(NO).C_6H_5$. Triphenylmethyl also attacks the free radicle. These two reactions furnish a perfect analogy with those occurring in the case of the di-aryl-hydrazyls and put the matter beyond doubt. Further, just as in the hydrazyls, the colour of the tetrazyl solutions deviates from Beer's dilution law.

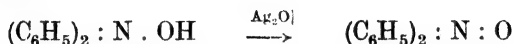
The most interesting of these new free radicles ia αα-diphenyl-β-picryl-hydrazyl: $(C_6H_5)_2N.N.C_6H_2(NO_2)_3$. It is stable in

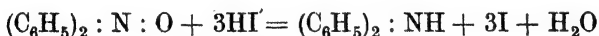
[1] Goldschmidt and others, *Ber.*, 1920, **53**, 44; 1922, **55**, 616; *Annalen*, 1924, **437**, 194.

the free state, forming crystals with a remarkable colour-similarity to those of potassium permanganate. Its solutions also have the tint of permanganate solutions. It can be boiled in toluene solution for some minutes without decomposition; and even in glacial acetic acid it remains relatively stable. Curiously enough, it does not react with nitric oxide in chloroform solution, though nitrogen peroxide readily attacks it. Hydroquinone reduces the hydrazyl to the corresponding hydrazine; and the colour-change caused by the reduction is so sharp that it can be employed for the estimation of the free radicle by titration of the hydrazyl with a hydroquinone solution of known strength.

5. *Derivatives containing Quadrivalent Nitrogen*

The oxidation of diphenyl-hydroxylamine with silver hydroxide yields a compound [1] which appears to have the formula shown below:

$$(C_6H_5)_2 : N . OH \xrightarrow{Ag_2O} (C_6H_5)_2 : N : O$$

Owing to its analogy in structure with nitrogen peroxide, this substance is termed diphenyl-nitrogen oxide. It is a crystalline compound, deep red in tint; and its vapour resembles that of nitrogen peroxide. It liberates iodine from potassium iodide:

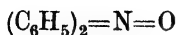
$$(C_6H_5)_2 : N : O + 3HI = (C_6H_5)_2 : NH + 3I + H_2O$$

With bromine it gives a halogen derivative of diphenylamine containing two bromine atoms attached to one phenyl nucleus and one bromine atom in the other. With nitrogen peroxide and triphenylmethyl it reacts readily. Concentrated mineral acids react with almost explosive violence upon the new compound.

The molecular weight determined cryoscopically in benzene corresponds to the monomolecular formula; and this apparently remains unaltered even in a mixture of ether and carbon dioxide, for at $-60°$ C. the substance can be recrystallized from ether and still retain its red colour.

One point of interest in connection with the compound is that its discovery throws considerable doubt upon a structure

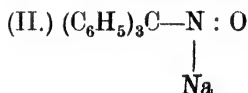
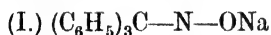
[1] Wieland and Offenbächer, *Ber.*, 1914, **46**, 2111.

suggested for nitrogen peroxide: for it is clear that diphenyl-nitrogen oxide resembles nitrogen oxide closely; and this tends to support the formula (II.) as against (III.).

$$(C_6H_5)_2{=}N{=}O \qquad O{=}N{=}O \qquad N\langle{}^{O}_{O}|$$

(I.) (II.) (III.)

The formation of $Br_3C_6H_2—NH—C_6H_4Br$ by the action of bromine upon the substance may point to the existence of a quinonoid grouping in the molecule; and it is possible that the case may be one of trivalent carbon instead of an example of quadrivalent nitrogen. Too little is known of the subject at present to make it worth while to speculate further.

The action of nitric oxide upon sodium triphenylmethyl takes place in stages. When the gas is passed into a solution of the sodium derivative, a colour-change from red-brown to faint bluish-red is observed, and a fine precipitate of the latter tint is thrown down. Further action of nitric oxide decolorizes both the solution and the precipitate; and the end-product is a yellowish-white body. On the basis of analyses, Schlenk regards the first formed compound as either (I) or (II). The first formula contains a divalent, the second a quadrivalent nitrogen atom.

(I.) $(C_6H_5)_3C—N—ONa$ (II.) $(C_6H_5)_3C—\underset{|\atop Na}{N} : O$

The final product is the sodium derivative of triphenylmethyl-nitroso-hydroxylamine: $(C_6H_5)_3C—N(NO)—ONa$.

E.—Monovalent Oxygen

When β-dinaphthol (I.) is oxidized with silver hydroxide, it yields a substance termed hydroxy-naphthylene oxide, to which the formula (II.) is ascribed. By treating this with potassium ferricyanide or indigo white, dehydroxy-dinaphthylene oxide is formed, which is supposed to have the structure (III.) or (III*a*.). This body, when dissolved in various solvents, shows colour phenomena akin to those observed in the triphenylmethyl series;

and, partly on this ground, it is assumed to dissociate into radicles [1] which have either of the structures (IV.) and (V.).

OH

HO

(I)

OH

O

(II)

O —— O

O O

III

=O O=

O O

IIIa

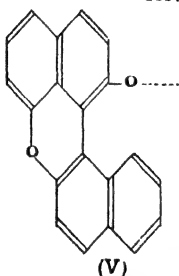
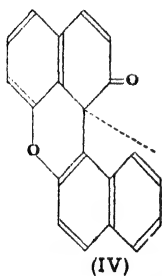
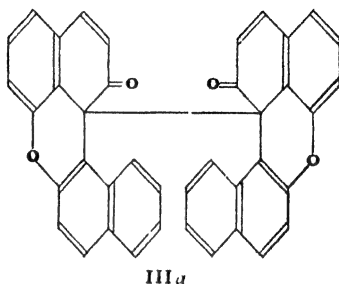
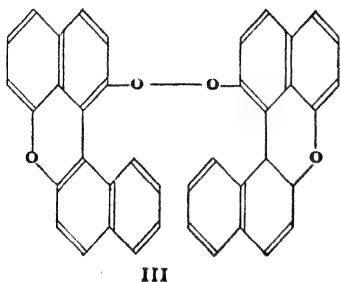
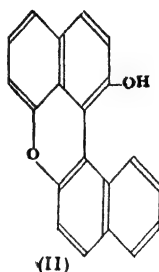
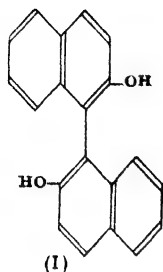
=O

O

(IV)

O ......

O

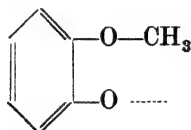
(V)

The supposed free radicle reacts readily with oxygen (though less rapidly than triphenylmethyl) forming an ochreous peroxide. Iodine also acts upon it more slowly than might have been anticipated. Hydrochloric acid decomposes it. Triphenylmethyl, cyclopentadiene, and pinene add themselves on to the radicle. Nitrogen peroxide forms an additive compound in ethereal or benzene solution, but does not attack the radicle to any extent in chloroform solution. When the substance is

[1] Pummerer and Frankfurter, *Ber.*, 1914, **46**, 1472; compare Pummerer and Cherbuliez, *Ber.*, 1914, **46**, 2957.

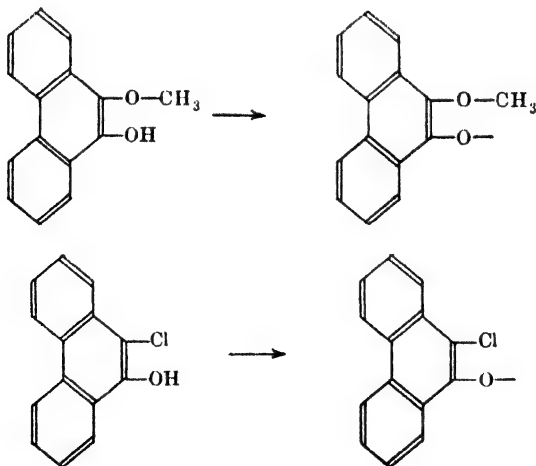
boiled in benzene solution it undergoes decomposition, yielding hydroxy-dinaphthylene oxide and dinaphthylene dioxide.

It will be seen from the above data that the compound is extremely complicated ; its reactions have not been fully studied ; and it may be well to refrain from laying too much stress upon its structure till its properties have been more thoroughly investigated.

Goldschmidt,[1] by oxidizing guaiacol with lead oxide, obtained a green solution which was immediately decolorized by hydroquinone or triphenylmethyl. He ascribed his results to the presence of the free radicle.

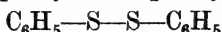
—O—CH_3
—O ....

More definite results [2] were obtained by him in the phenanthrene series during oxidations with potassium ferricyanide. The radicles shown below were formed, and the dissociation of the bimolecular saturated compound was found to reach 37 per cent. in the first case and 62 per cent. in the second case :

—O—CH_3 —OH ⟶ —O—CH_3 —O—

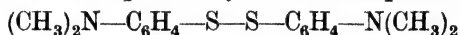
—Cl —OH ⟶ —Cl —O—

[1] Goldschmidt and Schmidt, *Ber.*, 1922, **55**, 3197.
[2] Goldschmidt and Steigerwald, *Annalen*, 1924, **348**, 202.

F.—Monovalent Sulphur

The oxidation of phenyl mercaptan yields phenyl disulphide,

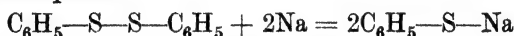
$$C_6H_5—S—S—C_6H_5$$

This substance in the solid state is colourless, but when it is dissolved in any indifferent solvent, the solution shows a faint yellow tinge, and the colour is intensified by raising the temperature. On cooling, the solution regains its original tint. This change in colour cannot be attributed to dissociation, according to Lecher,[1] since the solutions do not deviate from Beer's Law when examined in a colorimeter; so that the case is not parallel to that of triphenylmethyl in this respect.

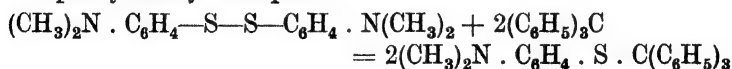
Further, in the case of *p*-dimethylanilido-disulphide:

$$(CH_3)_2N—C_6H_4—S—S—C_6H_4—N(CH_3)_2$$

an analogous colour change is observed when the solid substance is heated and cooled.

To explain these phenomena, Lecher suggests that the bond between the sulphur atoms is not broken but is merely weakened; and that the weakening of the valency and the development of colour are parallel changes.

Evidence of this weakening of the bond between the sulphur atoms was sought for in various reactions. For example, at ordinary temperatures or even at 80° C. sodium has little effect upon phenyl disulphide; but at 125° C. it reacts to produce sodium mercaptide:

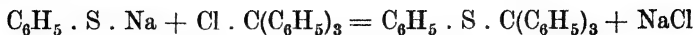
$$C_6H_5—S—S—C_6H_5 + 2Na = 2C_6H_5—S—Na$$

The weakness of the bond between the sulphur atom is also indicated by the interaction of *p*-dimethylanilido-disulphide and triphenylmethyl, which gives rise to 1-dimethylamido-phenyl-4-triphenylmethyl disulphide—

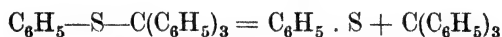
$$(CH_3)_2N \,.\, C_6H_4—S—S—C_6H_4 \,.\, N(CH_3)_2 + 2(C_6H_5)_3C$$
$$= 2(CH_3)_2N \,.\, C_6H_4 \,.\, S \,.\, C(C_6H_5)_3$$

These reactions suggest that under certain conditions it might be possible to obtain derivatives of monvalent sulphur; and though no actual isolation of such compounds has yet been achieved, their existence has been rendered probable by the following evidence.[2] Phenyl-triphenylmethyl sulphide can be

[1] Lecher, *Ber.*, 1915, **48**, 524.

[2] Lecher, *Ber.*, 1915, **48**, 524; 1920, **55**, 577.

obtained by the action of triphenyl-chloro-methane upon sodium phenyl mercaptide :

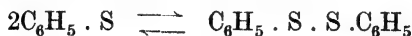
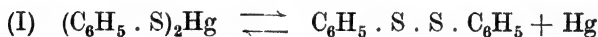
$$C_6H_5 . S . Na + Cl . C(C_6H_5)_3 = C_6H_5 . S . C(C_6H_5)_3 + NaCl$$

Now this sulphide becomes strongly yellow when heated in ethyl benzoate solution ; and an examination of the spectrum proves that triphenylmethyl is present. By shaking the solution in the air, the triphenylmethyl is oxidized, the solution becomes colourless ; and by further shaking in an indifferent atmosphere the yellow colour of triphenylmethyl reappears owing to a further decomposition of sulphide. The only way in which this reaction can reasonably be expressed is as follows :—

$$C_6H_5—S—C(C_6H_5)_3 = C_6H_5 . S + C(C_6H_5)_3$$

Further evidence [1] is found in the examination of mercury phenyl mercaptide, $C_6H_5 . S . Hg . S . C_6H_5$. It was observed by Dreher and Otto,[2] that this body, when heated, breaks up into mercury and phenyl disulphide ; and this suggests that heat loosens the bond between the sulphur and mercury atoms. On Lecher's view, the weakening of the valency force ought to be accompanied by a development of colour as the temperature rises. This actually proves to be the case. Whether dry or in solution, the mercaptide is colourless at ordinary temperatures but becomes yellow when heated, though no mercury separates from it under the experimental conditions employed.

Lecher suggests that the Dreher-Otto reaction is a reversible one which may take one of the two following courses :—

$$\text{(I)} \quad (C_6H_5 . S)_2Hg \rightleftharpoons C_6H_5 . S . S . C_6H_5 + Hg$$

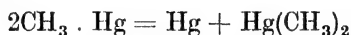
$$\text{(II)} \quad (C_6H_5 . S)_2Hg \rightleftharpoons 2C_6H_5 . S + Hg$$

$$2C_6H_5 . S \rightleftharpoons C_6H_5 . S . S . C_6H_5$$

If it can be proved that the reaction includes the two equilibria shown in (II), the existence of monovalent sulphur would be established ; but at present the subject is not beyond dispute ; and we must wait for further evidence before classing monovalent sulphur compounds along with the better-established cases of trivalent and divalent nitrogen.

[1] *Ibid.*, 1915, **48**, 1425 ; 1920, **53**, 577.
[2] Dreher and Otto, *Annalen*, 1870, **154**, 178.

G.—Monovalent Mercury

If a liquid ammonia solution of methyl mercury chloride, $CH_3 . Hg . Cl$, is electrolysed with a small cathode a highly attenuated opaque mass collects around the cathode.[1] When the mass is collected and allowed to warm up to near ordinary temperature it suddenly undergoes decomposition with the evolution of heat. The reaction appears to correspond to the following equation :—

$$2CH_3 . Hg = Hg + Hg(CH_3)_2$$

Other compounds containing other alkyl radicles and acidic groups behave similarly.

The material is black, like a finely divided metal ; and it is a good conductor of electricity. It does not amalgamate with mercury to any marked extent.

It is suggested by Kraus that this compound contains monovalent mercury ; and this is possibly the case. On the other hand, it is not improbable that it is actually $CH_3 . Hg . Hg . CH_3$; which might be formed at the small cathode just as persulphates are formed from sulphates under similar conditions at the anode. Further research will probably decide which of these views is correct.

H.—Free Alkyl Radicals

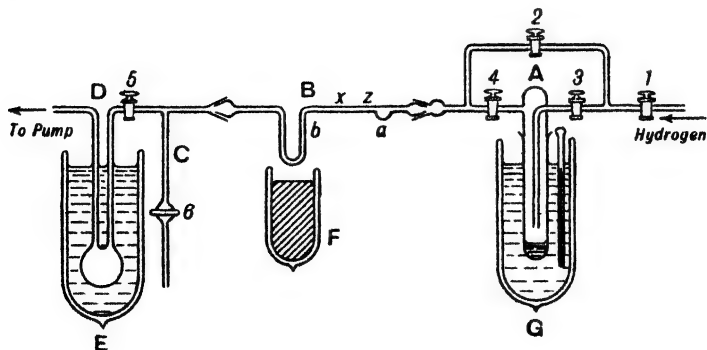
In recent years considerable attention has been given to the problem of proving the existence of free organic radicals. Free radicals have been postulated in explanation of many mechanisms of reactions, and consequently the demonstration of the existence of free alkyl groups is of outstanding interest. The major difficulty to be overcome was the great tendency of the radicals to combine with themselves or with other molecules to form normal compounds.

By working at very low pressures and removing the radicals as they were formed in a rapid stream of inert gas this difficulty was surmounted. The technique developed by Paneth and Hofeditz and described here has been employed in the majority of later investigations of free radicals.[2]

[1] Kraus, *J. Amer. Chem. Soc.*, 1913, **35**, 1732.

[2] Paneth and Hofeditz, *Ber.*, 1929, **62**, 1335 ; Paneth and Lautsch, *ibid.*, 1931, **64**, 2702 ; Paneth, *Trans. Faraday Soc.*, 1934, **30**, 179.

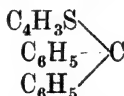
The experimental procedure for the production of methyl and ethyl radicals from the corresponding lead alkyls is as follows.

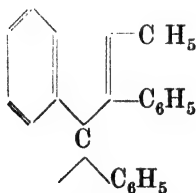
The apparatus, which is represented below in diagrammatic form, consisted of a shaped quartz tube (B) about 100 cm. long and 0·5 cm. internal diameter connected at one end to the vessel (A) containing lead tetramethyl, and at the other end to a mercury trap (D) and side tube (C). The whole apparatus was attached to a powerful vacuum pumping system. A metallic mirror of lead was deposited at the point (x) in tube (B) either by the decomposition of lead tetramethyl or by volatilizing metallic lead from the cavity (a). The system was evacuated to about 1·5 to 2 mm. and lead tetramethyl vapour from the vessel (A) cooled to −70° C. carried into tube (B) in a stream of hydrogen. The tube was heated to dull redness at the point (z) to decompose the lead tetramethyl. The lead was deposited just outside the hot zone and the methyl radicals passed on to attack and remove the lead at point (x). Lead tetramethyl was formed and frozen out of the stream of hydrogen in the tube (b) cooled in liquid air. The radicals methyl and ethyl also react with zinc, arsenic, antimony, bismuth, tellurium and other elements. It was shown that methane, ethane, ethylene or acetylene had no action on the deposited films either in the cold or when heated. The reactions must therefore be due to free radicals, which have a short but measurable life period. In an atmosphere of hydrogen at 2 mm. pressure it is estimated that the concentration of free methyl radicals falls to half value in about 0·006 second.

For a full account of other work in this field up to 1934 the reader is advised to consult the excellent text of F. O. Rice and K. K. Rice, *The Aliphatic Free Radicals.*

I.—Stability and Constitution

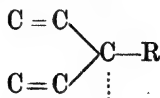
Though our knowledge of the free alkyl groups is rapidly extending, it is as yet too meagre to permit of any large generalizations being made about the factors which influence dissociation. One or two points, however, seem worthy of note.

In the group of substances allied to triphenylmethyl, the effect of replacing phenyl radicles by other radicles has been examined by various investigators.[1] From their results it is possible to draw the following inferences. In the first place, the presence of more than two phenyl groups attached to the trivalent carbon atom is shown to be unnecessary by the existence of Gomberg and Jickling's diphenyl-thienyl-methyl:

$$\left.\begin{matrix} C_4H_3S \\ C_6H_5 \\ C_6H_5 \end{matrix}\right\rangle C$$

This is confirmed by the fact that Kohler has obtained 1, 2, 3 triphenyl-indyl:

$$\begin{matrix} & & —C\ H_5 \\ C_6H_4 & \| & \\ & & —C_6H_5 \\ & C & \\ & & C_6H_5 \end{matrix}$$

wherein the trivalent carbon is directly attached to only two phenyl rings.

Inspection of this formula shows that it contains the group

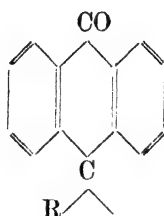
$$\left.\begin{matrix} C=C \\ C=C \end{matrix}\right\rangle C—R$$

[1] Kohler, *J. Amer. Chem. Soc.*, 1918, **40**, 228; Ziegler and Ochs, *Ber.*, 1922, **55**, 2257; *Annalen*, 1923, **434**, 34; Ziegler and Schnell, *ibid.*, 1924, **437**, 252; Conant and Sloan, *J. Amer. Chem. Soc.*, 1923, **45**, 2466; Conant and Small, *ibid.*, 1925, **47**, 3068; Gray and Marvel, *ibid.*, 2796; Gomberg and Jickling, *ibid.*, 1913, **35**, 446.

wherein the trivalent atom is distinguished by the dotted line. In 1, 2, 3-triphenyl-indyl, both the double bonds form part of a cyclic structure; but the same grouping occurs in triphenylmethyl itself, though in its case the double bonds belong to different rings; so that the grouping C : C—C—C : C is evidently the important factor and not the indene ring.

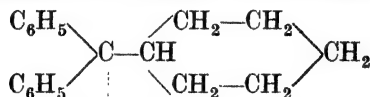
That R may be an aliphatic radicle has been shown by Conant and Small, who prepared derivatives of the following type:

CO

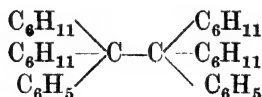
C

R

in which R represents normal hexyl or cyclohexyl.

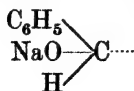
Ziegler and Schnell have obtained the free radicle

$$\begin{matrix} C_6H_5 \\ C_6H_5 \end{matrix} \!\!>\! C \!-\! CH \!<\! \begin{matrix} CH_2-CH_2 \\ CH_2-CH_2 \end{matrix} \!>\! CH_2$$

which establishes the fact that a cyclohexyl group has no inhibitive influence upon dissociation.

When, however, a second cyclohexyl group is substituted for one of the two phenyl radicles in the above formula, it was observed by Gray and Marvel that no dissociation could be detected, and that the compound behaved simply as if it had the formula:

$$\begin{matrix} C_6H_{11} \\ C_6H_{11} \\ C_6H_5 \end{matrix} \!\!>\! C \!-\! C \!<\! \begin{matrix} C_6H_{11} \\ C_6H_{11} \\ C_6H_5 \end{matrix}$$

In this structure there is no grouping C : C—C—C : C; from which it appears reasonable to infer that that particular grouping is essential to dissociation, so far as this group of compounds is concerned.

Among the metal-ketyls and their allies, the simplest case is that of the sodium derivative of benzaldehyde:

$$\begin{matrix} C_6H_5 \\ NaO \\ H \end{matrix} \!\!>\! C \cdots$$

What part the phenyl group plays in this structure is as yet undetermined. If it acts merely as a radicle incapable of yielding a hydrogen atom to the remainder of the molecule, so that enolization is prevented, then a compound of the structure $(CH_3)_3C . CHO$ should also give rise to a sodium derivative containing trivalent carbon. Possibly the pinacoline change may take its rise in some kindred phenomenon. If, on the other hand, the unsaturated character of the group attached to the aldehyde radicle is the dominant factor, then the compound $CH_3—C{\equiv}C—CHO$ might be made to yield a trivalent carbon atom when acted upon by sodium. It would be interesting to know the results in these two cases.

In the case of the divalent nitrogen compounds, a study has been made [1] of the constitutional factor's influence upon dissociation, with the following results. When the hexa-aryl tetrazanes of the formula $Ar_2N . N(Ar) . (Ar)N . NAr_2$ are compared with diacyl-tetra-aryl tetrazanes of the structure R . CO . N(Ar) . N(Ar) . (Ar)N . (Ar)N . CO . R, it is found that the acylated derivatives are less dissociated than the parent type. The influence of substitution is further noticeable in the following " order of dissociation," wherein the groups producing the least dissociation are placed at the bottom of the list :

↑ Dissociation
- Diacetyl-tetra (*p*-dimethylamino-phenyl)
- Dibenzoyl-tetratolyl
- Diacetyl-tetratolyl
- Dibenzoyl-tetraphenyl
- Diacetyl-tetraphenyl

J.—Conclusion

The abnormal compounds described in the present chapter, as well as their allies among the metal-ketyls and the triphenylmethyl series, cannot fail to suggest problems affecting the very bases of structural chemistry. Once the conception of free radicles is admitted, the long-tried dogma of the quadrivalence of carbon comes into the scales for a final test. It is doubtful if all the older ideas will be suddenly thrown aside. Much more probably we shall simply incorporate the idea of free radicles in our thinking and shall not trouble ourselves too

[1] Goldschmidt and others, *Ber.*, 1922, **55**, 616 ; *Annalen*, 1924, **437**, 194.

much over the incompleteness of our valency scheme. But the chemistry of free radicles, as it extends, is certain to have a marked influence upon our conception of valency. During the present generation, there has been a gradual process of facing fresh facts with regard to the chemical bonds, so far as organic chemistry is concerned. This first manifested itself in a preoccupation with residual affinity and partial valencies; then it showed itself in the attempt to bring electronic ideas to bear upon the carbon compounds; and finally, in recent times, the atomic theory of G. N. Lewis seems to have given us something much more definite and satisfactory than anything which preceded it. It is much too soon, as yet, to consider ourselves on firm ground; but when the further implications of the Lewis theory have been worked out and applied to unsaturated compounds in general, it seems not unlikely that we shall have a much clearer idea of a good many problems than we have at present.

The case of the free radicles is of special interest from the standpoint of Lewis's theory, since in the triphenylmethyl derivatives carbon acts as an ionogenic element, and thus we have a bridge built between the behaviour of the normal non-ionogenic carbon derivatives on the one hand and the ionizable molecules of salts upon the other hand. Lewis's theory, with its inclusive sweep, seems to offer most interesting possibilities in this region of chemistry.

CHAPTER XV

STRUCTURAL FORMULAE AND THEIR FAILINGS

An unbiassed survey of the fields covered by organic chemistry cannot fail to reveal to any critical mind the fact that our structural formulae are becoming less and less able to cope with the strain which modern research is placing upon them. It is true that for work-a-day purposes they still answer admirably; and from the point of view of teaching it is doubtful if anything better could be devised. But when we go into the matter beyond the mere surface, things are not so satisfactory as they may appear to the superficial observer. In the present chapter an attempt will be made to indicate briefly some points in the problem.

In the first place, it will be well to inquire as to the exact nature of our present-day formulae. According to Kekulé,[1] structural formulae were " decomposition " formulae :—

" Rational formulae are decomposition formulae, and in the present state of chemical science can be nothing more. These formulae give us pictures of the chemical nature of substances; because the manner of writing them indicates the atomic groups which remain unattacked in certain reactions. . . . Every formula which expresses definite metamorphoses of a compound is *rational*; that one of the different rational formulae is the *most rational*, which expresses the greatest number of the metamorphoses."

Couper,[2] on the other hand, put the case as follows :—

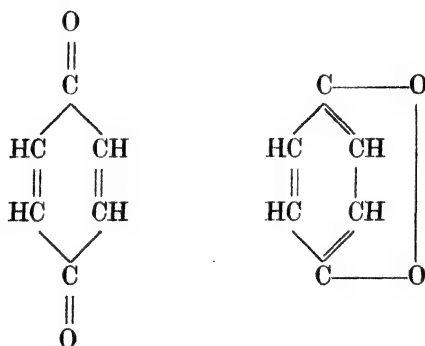
" Gerhardt . . . is led to think it necessary to restrict chemical science to the arrangement of bodies according to their decompositions, and to deny the possibility of our comprehending their molecular constitution. Can such a view tend to the advancement of science? Would it not be only rational, in accepting this veto, to renounce chemical research altogether?"

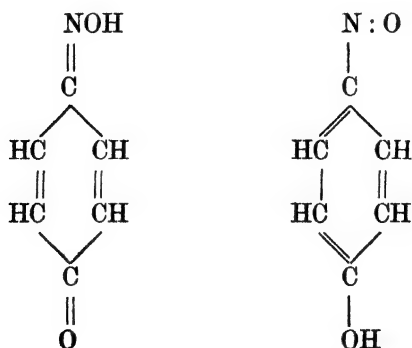
[1] Kekulé, *Annalen*, 1858, **106**, 149.

[2] Couper, *Phil. Mag.* 1858, IV., **16**, 107.

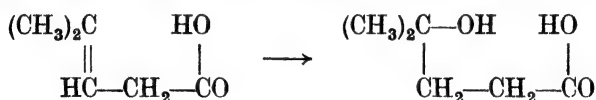
Thus, on the one side, we have Kekulé maintaining that graphic formulae are mere shorthand symbols by means of which we can easily and compactly express the results of our chemical experiments; whilst, on the other side, Couper claims that these ciphers give us the key to the actual mode of linkage of the atoms within the molecule. Let us take each of these views in turn and see how far they can be brought into agreement with modern conditions.

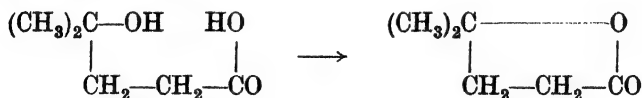
Regarded as pure reaction-formulae, it must be admitted that our present symbols fail at too many points for our intellectual satisfaction. If quinone be chosen as an example, we find that its formula is written in either of two ways:

```
        O
        ||
        C                 C——————O
       / \               //\     |
     HC   CH           HC   CH   |
     ||   ||           ||   |    |
     HC   CH           HC   CH   |
       \ /               \ //    |
        C                 C——————O
        ||
        O
```

each of which is a representation of its method of reacting with a certain reagent. But neither of these formulae allows us to foresee the fact that quinone monoxime will react as if it were nitroso-phenol:

```
       NOH               N:O
        ||                |
        C                 C
       / \               // \
     HC   CH           HC   CH
     ||   ||           |    ||
     HC   CH           HC   CH
       \ /               \\ /
        C                 C
        ||                |
        O                 OH
```

The number of facts of this type which have accumulated in recent years is considerable, and the result of this increase in knowledge has been remarkable. Instead of attempting to bring their formulae into harmony with the facts, organic chemists have been content to drag behind them a lengthening chain of implications, which they read into a formula; *e.g.*, we do not distinguish in our formulae between the two carbonyl groups of acetone and ethyl acetate, but we mentally interpret the two symbols differently. Thus, at the present time, it is quite conceivable that a student may be well acquainted with the meaning of all the ordinary chemical symbols, but may be hopelessly at sea with regard to the behaviour of a given compound; though to a more experienced chemist this is implicitly expressed in the formula which misleads the beginner.

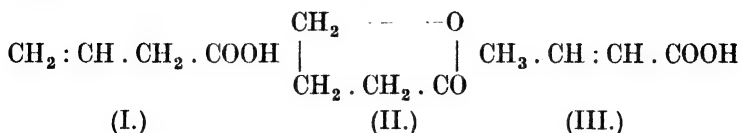
A concrete example will serve to bring out the amount of unexpressed material which we read into the ordinary formula. Let us consider the reactions of the unsaturated monobasic acids in presence of dilute sulphuric acid. In the first place, we assume that an addition of water to the double bond occurs:

$$\begin{array}{lcl} (CH_3)_2C \qquad\quad HO & & (CH_3)_2C{-}OH \quad HO \\ \quad \| \qquad\qquad\quad | & \longrightarrow & \quad | \qquad\qquad\qquad | \\ HC{-}CH_2{-}CO & & CH_2{-}CH_2{-}CO \end{array}$$

Now, we know from general experience that when one hydroxyl group lies in the 1,6-position to another in the same chain, water is usually eliminated with ease; so we should infer that the next step in the process would be such an abstraction of a water molecule:

$$\begin{array}{lcl} (CH_3)_2C{-}OH \quad HO & & (CH_3)_2C{-}{-}{-}{-}{-}{-}O \\ \quad | \qquad\qquad\qquad | & \longrightarrow & \quad | \qquad\qquad\qquad | \\ CH_2{-}CH_2{-}CO & & CH_2{-}CH_2{-}CO \end{array}$$

The formation of this compound is actually what does take place, so that in this case our inferences are justified; but let us apply the same series of ideas to another instance. Take the case of vinyl-acetic acid (I.), which contains the double bond in exactly the same position as in the other substance. Applying our experience as before, we should infer that the final product on heating with dilute sulphuric acid would be

the lactone (II.). In practice no such substance is formed, the product being the new unsaturated acid (III.).

$$CH_2 : CH . CH_2 . COOH \qquad \begin{array}{l} CH_2 \text{ --- } O \\ | \qquad\qquad | \\ CH_2 . CH_2 . CO \end{array} \qquad CH_3 . CH : CH . COOH$$

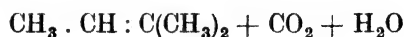
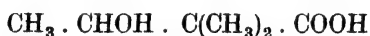
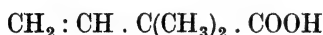
(I.) (II.) (III.)

But this does not bring us to the end of the possible reactions of this class of substances; for if we take the case in which two methyl groups are attached to a different carbon atom we find that the reaction follows yet another course:

$$CH_2 : CH . C(CH_3)_2 . COOH$$

$$\searrow$$

$$CH_3 . CHOH . C(CH_3)_2 . COOH$$

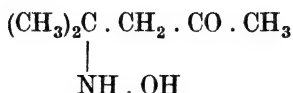
$$\searrow$$

$$CH_3 . CH : C(CH_3)_2 + CO_2 + H_2O$$

Thus, our formulae have ceased to be true reaction formulae, and may merely serve to mislead us if we attempt to draw any general conclusions from them.

Let us now turn to Couper's view of formulae, *viz.*, that they are to be regarded as true representations of the intimate structure of molecules. Here we appear to be upon safer grounds; but again we meet with drawbacks. If a formula represents the actual mode of linkage of the atoms in a molecule, how can we be certain of our results when we apply chemical reagents to the compound? Quinone, when treated with hydroxylamine, behaves as if it contained a carbonyl radicle; but if we employ phosphorus pentachloride as our reagent it acts as if quinone contained a benzene nucleus, since *p*-dichlorobenzene results. In this case, what is the true structure of quinone? If it be regarded as an equilibrium mixture of two compounds or as existing in two vibration-phases, what becomes of our "intimate structure of the molecule"?

Evidently, from Couper's point of view, the outside reagent is a disturbing factor not allowed for in our formulae. An example is furnished by the action of hydroxylamine upon mesity

oxide.[1] If the reaction is allowed to take place in a methyl alcoholic solution in presence of sodium methylate, the chief product is the substance formed by the addition of hydroxylamine to the double bond :

$$\begin{array}{l}(CH_3)_2\underset{\displaystyle NH.OH}{\overset{|}{C}}.CH_2.CO.CH_3\end{array}$$

But if, on the other hand, after exactly neutralizing hydroxylamine hydrochloride with sodium carbonate we allow it to act upon an alcoholic solution of mesityl oxide, we get the usual carbonyl group reaction, and mesityl oxime is formed :

$$(CH_3)_2C : CH . C(NOH) . CH_3$$

Thus in *alkaline* solution the ethylenic bond is stimulated into activity, while in *neutral* solution the carbonyl radicle appears the more reactive of the two.

From this it becomes clear that in order to ascertain the true " intimate structure of the molecule " we must find some way of determining it apart from extraneous materials. How is this possible ?

The recent developments in the study of physical properties of compounds indicate a means whereby the constitution of a body might be guessed without the necessity of applying disturbing reagents to it. At present our methods are not sufficiently advanced to permit us to establish molecular structure definitely by physical means alone ; but even to-day we can accomplish a good deal with the help of absorption spectra, magnetic rotation, refractive index, magnetic susceptibility, electric absorption, Tesla-luminescence spectra, X-ray diffraction, electron diffraction, optical rotatory power and dispersion ; and there seems to be little reason to despair of further progress.

It is at this point that we encounter the difficulty which has been responsible for wrecking a considerable amount of work in recent years. On the one hand, as we have seen, stand our " chemical " formulae which give us—incompletely enough, it must be confessed—a picture of the reactions of substances. On the other side, physical methods are showing

[1] Harries and Lellmann, *Ber.*, 1897, **30**, 230, 2726 ; Harries and Jablonski, *ibid.*, 1898, **31**, 1371 ; Harries, *Annalen*, 1904, **330**, 191.

us glimpses of the "intimate structure of molecules." Now a great mistake appears to have been made in assuming that both these things could be expressed by the same formulae. Our old reaction-formulae, though unable to cope with the difficulties in their own special field, have been imported willy-nilly into the problem of molecular structure, because we had nothing better to utilize there. The result has been something like the state of affairs which would reign in arithmetic if we insisted on using a mixture of Roman and Arabic notations in our calculations.

There is another region wherein our modern formulae are failing to meet the demands made upon them; the field of the unsaturated compounds. For present purposes, an unsaturated compound may be defined as a molecule which, without total disruption of its original structure, is capable of uniting with one or more fresh molecules. Now when this matter is considered in its broadest aspects, it is evident that what we term unsaturation is a specific and not a general property. We represent the unsaturation of an ethylenic linkage and of a carbonyl radicle by the same symbol, a double bond; and as far as the action of nascent hydrogen is concerned, this is quite accurate, for both the ethylenic linkage and the carbonyl group will attach to themselves two atoms of hydrogen. But when we use bromine instead of hydrogen, we find that only the ethylenic linkage reacts; for the carbonyl radicle remains unaffected by the reagent.

It is especially in this region of unsaturation that we find the limitations of our structural formulae most clearly marked. When we write a double bond between two atoms, we do not always mean the same thing. The double bonds in the cases of diphenyl-ethylene, ethylene, and fulvene certainly do not resemble one another chemically: in the first case the double bond is not attacked by bromine, which is taken up easily by the double bond of ethylene; but while the fulvene series are oxidized by air, ethylenic substances are not. Thus we have an increase in unsaturation (or reactivity as regards bromine and oxygen) as we go from diphenyl-ethylene through ethylene to the fulvenes; yet we symbolize all three unions between the carbon atoms of the double bonds in exactly the same way. It is perfectly evident that the amount of reactivity is different in

these three cases, and therefore the "chemical affinity," which gives rise to the reactions, must be different also.

But it is not only in the case of the double bond that we can trace this alteration in value of valencies; we can discover it in the case of single bonds as well. It is well known that in bromo-benzene, the bromine atom is held to the carbon atom of the nucleus more firmly than in aliphatic bromine derivatives. But if we nitrate the benzene ring, the bromine in the aromatic bromine derivative becomes as labile as that in the aliphatic one. This increase in reactivity can be due only to some change in the force which holds together the carbon and bromine atoms; in other words, the "valency-force" uniting bromine to carbon is stronger in bromobenzene than in nitro-bromobenzene.

From this point of view, investigations of the reactivities of certain atoms and groups in molecules are of the greatest importance. A considerable amount of work [1] in this direction has already been carried out; but a vast field lies open to research in this branch of the subject.

[1] See among others, Clarke, *Trans.*, 1911, **99**, 1432; 1912, **101**, 1788; Harper and Macbeth, *J*,. 1915, **107**, 87; Macbeth, *ibid.*, 1824; Petrenko-Kritschenko, *J. pr. Chem.*, 1900, [2], **61**, 431; Petrenko-Kritschenko and Kantscheff, *Ber.*, 1906, **39**, 1452; Senter, *J.*, 1909, **95**, 1827; *J.*, 1910, **97**, 1623; Stewart, *J.*, 1905, **87**, 185, 410. An interesting paper by Tschitschibabin (*J. pr. Chem.*, 1912, **86**, 381) on "The Valency of Carbon Atoms in So-called 'Unsaturated' Compounds" may be brought to the notice of the reader in this connection.

CHAPTER XVI

SOME APPLICATIONS OF ELECTRONICS TO ORGANIC CHEMISTRY

1. *Introductory*

THE first quarter of the twentieth century will doubtless be noted in the history of chemistry as the period when our ideas of valency changed their form and drew nearer than ever before to the underlying reality. Up to that period, modern chemistry had always suffered from a lack of unity. In early days, the vitalistic ideas demanded a segregation of naturally-synthesized organic compounds from the remainder of the subject; and the science was arbitrarily divided into "organic" chemistry and "inorganic" chemistry. This cleavage had hardly been healed by the work of Wöhler when a fresh line of fission made its appearance. The multiplicity of the carbon derivatives and their difference from the metallic salts soon led to a separation of the two classes from one another; and thus once again chemistry became a kind of dual monarchy. The constitutional formulae of Kekulé at first seemed to offer the hope that all chemical compounds might eventually be brought back under a single head, since his symbols could be made to fit the simpler inorganic compounds like sulphuric acid. Before much time had been wasted in this attempt, however, a fresh line of division appeared with the ionic theory of solution; and compounds came to be classified as electrolytes or non-electrolytes, a method of demarcation which cut clean across the earlier grouping, since it included the organic acids and their salts along with the inorganic salts and acids.

At this period, a contest became focussed upon the two modes of regarding chemical affinity. In the ionic reactions, the processes were obviously electrical in their nature and were associated with the occurrence of definite electrical units. All

the simpler salts, bases, and acids could be regarded as being held together by purely "polar" forces, since in their reactions the governing factors appeared to be charges of positive and negative electricity. But, on the other hand, the far more numerous organic compounds refused to be explained on a "polar" basis. So far as could be ascertained, the reactions of organic chemistry differed completely in nature from the rudimentary processes which served to account for the behaviour of ionizable materials.

At this stage, little hope of ultimate harmony appeared likely. The extreme ionists seemed to wish for a return to the rigid "polar" ideas of Berzelius, extending the idea of ions throughout the whole range of the carbon compounds; but as few of them had any thorough knowledge of the complexities of organic chemistry, their arguments failed to convince the specialists in that branch of the science. The more enthusiastic exponents of Kekulé's "non-polar" ideas, on the other hand, held the firm belief that the intimate constitution of the ferrocyanides, for example, could be expressed satisfactorily by "non-polar" bonds; and the fact that such symbolism perforce omitted from its scope the ionic character of the substances, seemed to have little weight in their minds.

The unfortunate pretensions of the extremists in both schools did much to hinder progress. Instead of trying to find some common ground upon which both sides could meet and co-operate, each group endeavoured to annex the field properly belonging to the other. To Ostwald, who did not believe in the real existence of atoms, structural chemistry could appear only in the guise of fantastic nonsense; and he calmly proposed to throw overboard the whole graphic symbolism and replace it by a series of purely mathematical expressions which he believed would serve as well, if not better.* The extremists in the other camp were hardly wiser; and some of the attempts to write graphic formulae for complicated inorganic compounds proved too much for even confirmed "constitutionalists."

J. J. Thomson's work on electrons marked the opening of a fresh avenue in chemistry; but unfortunately the initial

* He prudently left the task of discovering these mathematical expressions "to younger colleagues" and refrained from adventuring into the field himself.

hypotheses put forward by him and others had incorporated in them an element based on " direction." For example, methane might be represented as being formed by four electrons leaving the carbon atom and fixing themselves on the hydrogen atoms, or by an electron leaving each of the hydrogen atoms and coming to rest on the central carbon atom :

Thus methane should exist in two " electromeric " forms ; whereas only a single methane is known in practice. In more complex compounds the number of possible " electromers " rose to very high figures ; and the only way of reconciling theory and practice was to assume that most of the arrangements were unstable systems incapable of real existence.

A further step in advance was marked by Rutherford's proof that the atom consisted of a positive nucleus surrounded by a group of neutralizing electrons ; and Moseley's researches brought out the relationship between the number of positive charges on the nucleus and the atomic number of the element.

2. *The Theory of G. N. Lewis*

It was not until 1916 that a model atom was suggested which fitted our chemical requirements. G. N. Lewis [1] proposed to regard the atomic electronic system as a cubical arrangement of which the corner-points could be occupied by electrons. Since organic chemistry is mainly concerned with atoms belonging to the first two series in the Periodic Table, this cubical model is sufficient for our present purpose, and it is unnecessary to discuss the further extension of the theory which was made by Langmuir.

According to G. N. Lewis, hydrogen is representable by a nucleus carrying one positive charge, attached to which there is a single electron, making the system electrically neutral. The electron, is detachable and when it is removed, the " proton "

[1] G. N. Lewis, *J. Amer. Chem. Soc.*, 1916, **38**, 762.

of the nucleus becomes what is generally known as a hydrogen ion.

The helium system of Lewis consists of a nucleus carrying two positive charges and neutralized by two electrons. As helium is an inert gas, this model system must be assumed to be extremely stable and the electrons in it are not detachable.

The lithium atom of Lewis is composed of a triply-charged nucleus surrounded by a neutralizing system of three electrons. In practice, lithium salts yield only monovalent lithium ions, so that evidently one of the three electrons differs from the other two. This Lewis expressed by the following model. At the centre is the nucleus carrying three positive charges. Associated with this is a group of two electrons—the helium complex. Outside this lies the detachable electron of the lithium system. At this point the cubical system comes into force, and the detachable electron of lithium is supposed to rest at the corner of a cube which contains the lithium complex of two electrons and which has at its centre the triply-charged positive nucleus.

As we proceed from element to element through the first series of the Periodic Table, electron after electron is fitted into the vacant corners of the cube, and in each case a corresponding positive charge is added to the nucleus. Thus the outer shells of the atoms can be represented by the following diagram (Fig. 1):

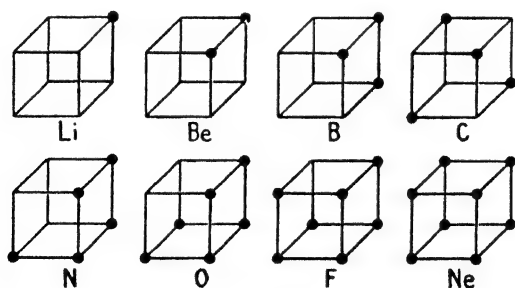



Fig. 1.

With the neon atom, all the corners of the cube are occupied by electrons; and since neon is an inert gas, this octet is assumed to form a stable system which will neither take up nor part with electrons. In order to form the sodium atom, a fresh cube,

external to the neon cube, must be commenced; and a single electron must be placed at one of its corners. Thereafter, the model atoms of remaining elements, sodium, magnesium, aluminium, etc., are formed by adding more and more electrons to the cube until with argon the whole second octet is completed and a stable system produced.

The picture of the model atom is completed by adopting Aston's view that the atomic nucleus contains protons equal in number to the figure representing the true atomic weight and intimately united with electrons sufficient to leave a surplus positive charge equivalent to the atomic number.

Since the carbon atom is of special interest in organic chemistry, it will be sufficient to choose it as an example. The atomic weight of carbon is 12, therefore we assume twelve protons in the nucleus. The atomic number of carbon is 6, so six electrons are inserted into the nucleus, leaving the nuclear system with a surplus charge of 6 (the atomic number). Now for electrical neutrality, we need six extra electrons. These are grouped around the nucleus as follows. In an internal region lie the two electrons of the helium complex. Outside these lies the cubical grouping and at four corners of the cube lie the remaining four electrons. This leaves four unoccupied corners; and these are ready to receive electrons by chemical combination of the carbon atom with other atoms, thus completing the octet which is the stable, inert grouping in the cubic atom. For example, methane is represented by the introduction into the carbon system of four electrons derived from four hydrogen systems, and the residual protons of the four hydrogen atoms are retained by electronic forces.

Since this cubical grouping fails to represent the normal tetrahedral arrangement postulated in organic chemistry to account for the asymmetric carbon atom, G. N. Lewis assumes that the electrons can shift from the corners along the edges of the cube so that in methane, for example, they would move from the points marked with faint circles to the positions indicated by the black circles * in the following diagram and thus fall into tetrahedral grouping (Fig. 2):

* The reason for eight electrons being shown here will be apparent when the formula of methane is discussed. See p. 325.

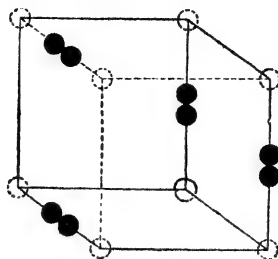



FIG. 2.

It is now necessary to examine the interpretation which G. N. Lewis's theory places upon valency and to show how by his model atom the apparently antagonistic ideas of polar and non-polar bonds can be harmonized.

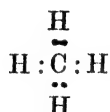
From the point of view of organic chemistry, the main basis of the Lewis theory can be stated thus. (1) Electrons may be "shared" between two atoms, thus belonging jointly to both the atomic systems involved. Such "shared electrons" are found in pairs in carbon compounds. (2) Electrons may be wholly transferred from one system to another. (3) When electrons are introduced into the systems of atoms belonging to the first series of the Periodic Table, the tendency is to produce an octet of electrons (a "pseudo-neon" system) in the outer sphere of the atom; and the combination of atoms tends always to produce, if possible, a series of octet groups of electrons.

Representing electrons by dots and assuming the existence of the appropriate positive charges in the nuclei, it is possible to express the various systems quite simply and indicate the various results which follow from Lewis's postulates.

Take the molecule of hydrogen as a first example. The atom of hydrogen can be written as $H^{\cdot}$, the H representing the nuclear proton and the dot the electron. Now when two atoms of hydrogen combine to form molecular hydrogen, they can do so by simply sharing the two electrons and H : H would be the symbol for H_2. Here either proton may be regarded as having attached to it two electrons, so that by the sharing of the pair of electrons two "pseudo-helium" inert groupings are obtained. This gives an example of electron-sharing in its simplest form; and it will be seen that the "shared" electrons occur in pairs.

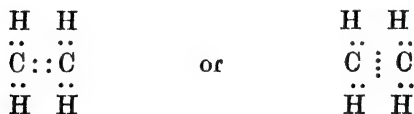
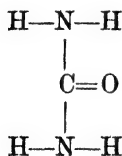
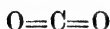
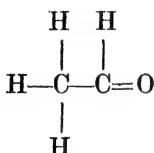
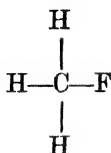
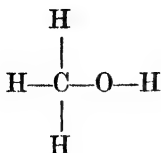
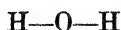
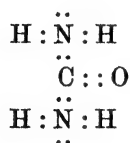
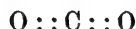
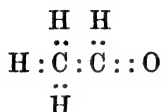
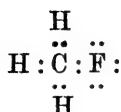
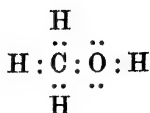
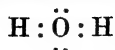
Also, since molecular hydrogen does not dissociate electrolytically, it is clear that "shared electrons" do not constitute a polar bond.

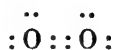
Turn next to the molecule of methane. The carbon atom has four electrons in its cubic system; and there are four electrons in the four hydrogen atoms. This makes a total of eight—the inert octet. Each of the hydrogen atoms inserts its electron into one of the vacant corners of the carbon cube, thus completing the octet round the carbon nucleus; but by this means each of the four carbon electrons becomes part of a hydrogen system, bringing it up to the "pseudo-helium" duplet. Thus the electronic system of methane can be represented by the symbol:

$$\begin{array}{c} \mathrm{H} \\ \cdot\cdot \\ \mathrm{H : C : H} \\ \cdot\cdot \\ \mathrm{H} \end{array}$$

wherein the carbon nucleus is surrounded by eight electrons, which simultaneously serve to complete the four duplets of the hydrogen "pseudo-helium" systems.

Inspection of this symbol reveals at once that it can be derived from the ordinary graphic formula of methane by writing a duplet of electrons for each Kekulé bond; and from this it follows that the non-polar bonds of the carbon compounds are represented on the Lewis theory by *two electrons jointly shared* between two electronic systems.

By analogy, an ethylenic linking should be represented on Lewis's system by *two* pairs of electrons shared between the two carbon systems which are united by the ethylenic bond:

$$\begin{array}{ccc} \mathrm{H} & & \mathrm{H} \\ \cdot\cdot & & \cdot\cdot \\ \mathrm{C} & :: & \mathrm{C} \\ \cdot\cdot & & \cdot\cdot \\ \mathrm{H} & & \mathrm{H} \end{array} \qquad \text{or} \qquad \begin{array}{ccc} \mathrm{H} & & \mathrm{H} \\ \cdot\cdot & & \cdot\cdot \\ \mathrm{C} & \vdots & \mathrm{C} \\ \cdot\cdot & & \cdot\cdot \\ \mathrm{H} & & \mathrm{H} \end{array}$$

One or two other examples of these formulae will familiarize the reader with the electron-pairs and the octet groups. It must be borne in mind that the numbers of electrons in the cube are respectively, 4 for carbon, 5 for nitrogen, 6 for oxygen, and 7 for fluorine.

Very little consideration is required to reveal the atomic conditions necessitating electron-sharing. If the total number of electrons in the outermost spheres of all the atoms in a molecule is not divisible by eight, then some of the electrons must be shared between the atomic systems in order to complete the stable octets. For example, the cube of the fluorine atom has seven electrons in it; so that the two fluorine cubes of the fluorine molecule have 14 electrons in all. In order to construct two complete octet systems from 14 units, it is obvious that two electrons must be shared between the two systems :—

$$:\ddot{\underset{\cdot\cdot}{F}}:\ddot{\underset{\cdot\cdot}{F}}: \qquad\qquad :\ddot{O}::\ddot{O}:$$

The oxygen molecule must contain a system of four shared electrons (as shown above) if two complete octets are to be constructed from the available twelve electrons.

Hitherto we have been considering Lewis's representation of non-polar bonds; but it is now necessary to turn to the other side of his theory and show how it applies to ionogenic systems. Suppose that the various atoms associated in the molecule contain a total number of electrons which is exactly divisible by 8. Then clearly a system of this kind can arrange itself so as to form a series of complete octets without any electron-sharing. In this case, there are no non-polar bonds present, and the system represents two or more ions held together by purely electrostatic forces.

The simplest case is that of hydrofluoric acid. Since a hydrogen system has one electron and the fluorine system has seven, the two together will suffice to form the complete octet and might be written thus:

$$\mathrm{H}:\ddot{\underset{\cdot\cdot}{\mathrm{F}}}:$$

This would represent the sharing of two electrons between the hydrogen and flourine systems. But if we assume, with Lewis, that the process is not arrested at this stage, but that, instead, the hydrogen electron passes over into the fluorine system in order to make an independent octet of that system, then we have a case of *electron-transference*. The two systems will still remain in contiguity, because the fluorine system now has one excess negative charge (due to the engulfed electron), whilst the hydrogen proton (having lost its companion electron) has a free positive charge. We have, in fact, two ions which will attract each other by simple electrical affinity; and which, in the proper circumstances, may drift apart thus:

$$\left[\mathrm{H}\right]^{+} \qquad\qquad \left[:\ddot{\underset{\cdot\cdot}{\mathrm{F}}}:\right]^{-}$$

Hydrogen ion. Fluorine ion.

It is now clear that Lewis's ideas can be used to symbolize both polar and non-polar types of union; the non-polar type being represented by electron-sharing, the polar type by electron-transference: and, further, that the two types may shade into one another in such a way as to account for the carbonium salts

derived from triphenylmethane,[1] wherein ionogenic power is manifested by bonds which normally might be regarded as non-polar in character.

An interesting application of the Lewis theory is to be found in the cases of beryllium hydroxide, dihydroxy-methane, and formic acid. In the first case, the molecule yields basic ions, in the second example the decomposition is spontaneous and produces water and the neutral substance formaldehyde, whilst formic acid yields hydrogen ions. These three processes are represented as follows on the octet symbolism.

```
          ..       ..               ..                   ..
(I.)   H : O : Be : O : H  ⟶   H : O :   +   Be   +   : O : H
          ..       ..               ..                   ..
                                   (−)       (+ +)        (−)

              H                                  H
          ..  ..  ..                ..           ..
(II.)  H : O : C : O : H   ⟶    H : O : H   +    C : : O
          ..  ..  ..                ..           ..
              H                                  H

              H                        H
        ..    ..  ..             ..    ..  ..
(III.)  O : : C : O : H   ⟶      O : : C : O :   +   H
        ..        ..             ..        ..
                                          (−)       (+)
```

In (I.), it is evident that the molecule contains two complete octets centred in the oxygen atoms; and these might separate from the beryllium atom—which is not the nucleus of an octet —and so form two hydroxyl ions. In Case (III.), the carbon octet is present in the centre of the molecule so that a breakdown of type (I.) could occur only by the rupture of this octet. Since the octet is assumed to be a stable grouping, this collapse is not to be expected. Instead, electron-transference occurs in such a way as to maintain the maximum number of octets, and a hydrogen ion is formed. In Case (II.), either of the hydroxylic hydrogens might be expelled as an ion; but here it would find a hydroxyl radicle (not present in formic acid) which it might attack in order to form water: and thus the whole system would suffer decomposition as shown.

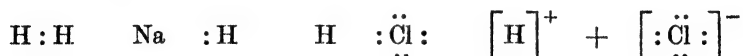
3. *Octet Stabilities*

In his initial exposition of his theory, G. N. Lewis pointed out that " great as the difference is between the typical polar

[1] Walden, *Z. physikal. Chem.*, 1903, **43**, 442.

and non-polar substances, we may show how a single molecule may, according to its environment, pass from the extreme polar to the extreme non-polar form, not *per saltum*, but by imperceptible gradations, as soon as we admit that an electron may be the common property of two shells. . . . The pair of electrons which constitutes the bond may lie between the two atomic centres in such a position that there is no electrical polarization or it may be shifted towards one or the other atom in order to give to that atom a negative, and consequently to the other atom a positive charge." [1]

Lewis illustrated this variation in the situation of the electron-pair by means of the hydrogen molecule, the molecule of sodium hydride, the hydrogen chloride molecule, and the ions of hydrochloric acid :—

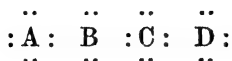
$$\mathrm{H:H} \qquad \mathrm{Na\quad :H} \qquad \mathrm{H\quad :\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:} \qquad \left[\mathrm{H}\right]^{+} + \left[:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{Cl}}}:\right]^{-}$$

In the hydrogen molecule the electron-pair is placed symmetrically between the two atoms. In sodium hydride, the electrons lie nearer to the hydrogen than to the sodium, making the hydrogen negative. In hydrogen chloride the electron-pair is shifted towards the chlorine, endowing the hydrogen with a positive charge ; and in presence of a polar solvent the chlorine assumes full possession of the electrons and complete ionization ensues.

This idea has been utilized by Kermack and Robinson [2] in order to give a physical basis to their views on alternative polarity in carbon chains. According to their hypothesis, if in the system $:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{A}}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{B}}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{C}}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{D}}}:$ the octet surrounding A becomes unstable from any cause, external or internal, this will automatically involve more or less appropriation of the two electrons shared with B, the octet of which is therefore unstable and tends to disintegrate. The stability of the B octet having thus been shaken, the atom C will be able to appropriate the electron-pair common to B and C and produce around itself a stable octet, in

[1] See G. N. Lewis, *Valence*, p. 83 (1923), and also his earlier papers, *J. Amer. Chem. Soc.*, 1916, **38**, 762 ; *Proc. Nat. Acad. Sci.*, 1916, **2**, 586.

[2] Kermack and Robinson, *J.*, 1922, **121**, 427 ; compare Lowry, *J.*, 1923, **123**, 822.

the formation of which the octet of D is in turn disintegrated. This can be represented crudely as follows :

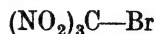
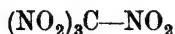
```
 ..   ..  ..   ..
:A:  B   :C:  D:
 ..   ..  ..   ..
```

Here, as Lewis points out,[1] the change does not result in any of the atoms having an integral number of units of charge, since this is found only in ions ; but nevertheless alternate atoms in the chain have become either more akin to positive ions or to negative ions than they were before the electron-shift occurred.

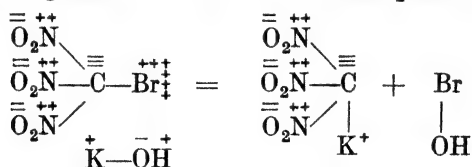
The most convincing piece of evidence yet brought forward to show the truth of this speculation has been furnished by Macbeth and his collaborators.[2] Since the octet representation would be too intricate for easy reading in this case, it will be better to utilize the symbolism used by Macbeth and mark "pseudo-positivity" by means of a + sign and "pseudo-negativity" by a — sign. The facts of the case are as follows. (1) When tetranitromethane, $(NO_2)_4C$, is acted on by potassium hydroxide, one nitro-group is eliminated and the potassium salt of nitroform is produced. A nitro-group is removed also by the action of titanous chloride, hydrazine, potassium ferrocyanide, and potassium sulphite. (2) The halogen atom of chloro-trinitromethane or bromotrinitromethane is readily removed by potassium hydroxide, yielding the potassium salt of nitroform. The halogen atom is also removed with ease by alkaline reducing agents, potassium ferrocyanide, and titanous chloride. (3) One bromine atom of dibromodinitromethane is removed by potassium hydroxide, potassium ferrocyanide, or hydrazine. Titanous chloride reduces the nitro-groups but leaves the halogen intact. (4) Chloropicrin, when treated with hydrazine, very slowly loses one chlorine atom in the cold. Potassium ferrocyanide is without action. Titanous chloride reduces the nitro-group but leaves the halogens untouched. (5) Monobromonitromethane and dibromonitromethane are unacted on by hydrazine or potassium ferrocyanide. Titanous chloride reduces the nitro-group without removing the halogen.

[1] G. N. Lewis, *Valence*, p. 83 (1923).

[2] Henderson and Macbeth, *J.*, 1922, **121**, 892 ; Hirst and Macbeth, *ibid.*, 904 ; Macbeth, *ibid.*, 1116.

This series of results obviously displays a regular gradation in the activity of the halogen atoms and also of the nitro-groups. In the cases of tetranitromethane and bromo-trinitromethane

$$(NO_2)_3C—NO_2 \qquad\qquad (NO_2)_3C—Br$$

the nitro-group and the bromine atom are not only removed, but they are replaced by the strongly positive potassium atom. This Macbeth accounts for by assuming that the oxygen atoms of the three nitro-groups exert a polarizing influence on the chain with the result that the nitrogen atoms become positively polarized, the carbon atom is negatively polarized, and the terminal nitro-group or bromine atom becomes positively polarized. Representing the effect of each oxygen atom by a minus sign and indicating its polarizing effect on its neighbouring atom by an equal number of positive signs, the result in bromo-trinitromethane is as shown below; and the reaction with potassium hydroxide finds a simple expression, since the positive potassium is seen to be replacing a bromine atom in which there is a great accumulation of induced positive polarity.

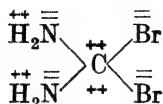
$$\begin{array}{lcl}
\overset{\equiv}{O_2}\overset{++}{N}\diagdown & & \overset{\equiv}{O_2}\overset{++}{N}\diagdown \\
\overset{\equiv}{O_2}\overset{++}{N}—\overset{\equiv}{C}—\overset{+++}{Br}{\scriptstyle\substack{+\\+\\+}} & = & \overset{\equiv}{O_2}\overset{++}{N}—\overset{\equiv}{C} \quad + \quad Br \\
\overset{\equiv}{O_2}\overset{++}{N}\diagup & & \overset{\equiv}{O_2}\overset{++}{N}\diagup \,| \qquad\quad | \\
\qquad \overset{+}{K}—\overset{-\,+}{OH} & & \qquad\quad K^{+} \qquad OH
\end{array}$$

Macbeth regards this induced positivity of the halogen atom as the reason for its ready removal by reducing agents such as potassium ferrocyanide and hydrazine.

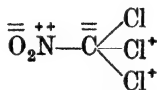
Now, on Macbeth's hypothesis, in dibromodinitromethane and dichlorodinitromethane, the halogen atoms must have much less induced positivity since only two nitro-groups are influencing them here, as against three in bromotri-nitromethane. Not only so, but the polarizing influence of the two groups is further diminished since it is distributed over two halogen atoms, as shown in the scheme given by Macbeth:

$$\begin{array}{ccc}
\overset{\equiv}{O_2}\overset{++}{N}\diagdown & & \diagup\overset{++}{Br} \\
 & \overset{\equiv}{\underset{=}{C}} & \\
\overset{\equiv}{O_2}\overset{++}{N}\diagup & & \diagdown\overset{++}{Br}
\end{array}$$

Here, obviously, each bromine atom has only one third of the induced positive polarity which it possesses in the formula

given above for bromotrinitromethane. Titanous chloride fails to attack the bromine atoms and reduces the nitro-groups instead. Once the nitro-groups are reduced, the whole polarity-chain in the molecule is inverted, and the titanous chloride is unable to remove the halogen atoms :

$$\begin{array}{c} \overset{++\ =}{H_2N} \searrow \overset{++}{} \swarrow \overset{=}{Br} \\ \qquad C \\ \overset{++\ =}{H_2N} \nearrow \underset{++}{} \nwarrow \overset{=}{Br} \end{array}$$

Finally the case of chloropicrin, is represented by Macbeth in the following scheme :

$$\overset{=\ ++}{O_2N}—\overset{=}{C}\begin{array}{l} \diagup Cl \\ —Cl^{+} \\ \diagdown Cl^{+} \end{array}$$

Here the induced positivity on the halogen atoms is only one-sixth of that allotted in the case of bromotrinitromethane; and even so, one chlorine atom has no induced positivity at all. In this case potassium ferrocyanide has no action and even hydrazine works very slowly.

It must be admitted that Macbeth's explanation goes hand in hand with the facts ; and this series of reactions furnishes considerable strength to the supporters of the induced polarity idea. Macbeth has extended similar explanations to other classes of compounds. Many workers have extended these ideas and the reader is referred to the excellent accounts published.[1]

4. *Ionization and Chemical Action*

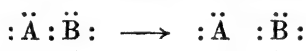
In a foregoing section it has been shown that by adopting Lewis's views it is possible to depict the comparatively rigid structures of organic compounds and also the looser complexes formed by the association of ions ; and it may be recalled that the reactions of organic compounds are in general fairly slow, whereas the interactions of ions are instantaneous.

[1] R. Robinson, *Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions*, The Institute of Chemistry of Great Britain and Ireland, 1932 ; C. K. Ingold, *Principles of an Electronic Theory of Organic Reactions, Chemical Reviews*, Vol. XV., No. 2, October, 1934 ; Waters, *Physical Aspects of Organic Chemistry*, G. Routledge & Sons, Ltd., London, 1935 ; Remick, *Electronic Interpretations of Organic Chemistry*, Chapman & Hall, Ltd., 1943 ; R. Robinson, Faraday Lecture, Chemical Society, 1947.

So far back as 1881, Helmholtz [1] voiced the idea that all substances were electrolytes despite the differences among them. In 1885, Armstrong [2] hazarded the conjecture that chemical reaction was " reversed electrolysis " ; and the work of H. B. Baker [3] has proved that some extremely dry reagents hardly interact at all, though they immediately combine as soon as a trace of water is added to the system. Lapworth [4] suggested in 1901 that reactivity may depend upon the existence of ions or the manufacture of ions by the rupture of non-polar bonds.

With the recent applications of the theory of G. N. Lewis to clarify the representation of molecules and ions, it has been possible to develop these tentative suggestions of Armstrong and Lapworth in a more detailed fashion ; and some account will now be given of Lowry's interpretation of the courses of some typical reactions in organic chemistry.[5]

According to Lowry, chemical reaction takes place between ions, free or bound ; and the process is the same in both organic and inorganic chemistry. But this implies that the non-polar bonds of the organic compounds must be capable of yielding ions in some manner ; and Lowry suggests that a duplet of electrons shared between two atoms may adhere as a whole to one or other of the atomic systems when these are pulled apart.[6] In this way one complete octet and one sextet would be produced :

$$:\ddot{\underset{\cdot\cdot}{A}}:\ddot{\underset{\cdot\cdot}{B}}: \longrightarrow :\ddot{\underset{\cdot\cdot}{A}} \quad :\ddot{\underset{\cdot\cdot}{B}}:$$

This is in agreement with Lewis's view on the peculiar tendency of electrons to associate in pairs.* Further it, provides a possible explanation of the hitherto incomprehensible phenomena observed by Walden,[7] who found that tin, sulphur, phosphorus, antimony, chlorine, bromine, and iodine when dissolved in liquid sulphur dioxide or arsenic trichloride yielded solutions

[1] Helmholtz, *Vortrage u. Reden*, II., 274 (1896).
[2] Armstrong, *P.*, 1885, **1**, 39.
[3] H. B. Baker, *J.*, 1902, **81**, 400.
[4] Lapworth, *J.*, 1901, **79**, 1266.
[5] Lowry, *Lecture to the Institut international de chimie Solvay*, April, 1925 ; compare Lowry, *Bull. Soc. chim.*, 1924 (4), **36**, 815, 905 ; 1926 (4), **39**, 203 ; *Nature Supplement*, May 29, 1926, p. 33 ; *J. Soc. Chem. Ind.*, 1925, **44**, 970.
[6] Compare G. N. Lewis, *Valence*, p. 83 (1923).
* If this pairing were not assumed, then the system shown above might be assumed to break up into two septets of electrons.
[7] Walden, *Z. physikal. Chem.*, 1903, **43**, 385.

with marked electrical conductivities. It accounts also for the conducting power shown by solutions of triphenyl-chloromethane.[1] Finally, it furnishes an interpretation of the fact that the union of ethylene with bromine can be markedly retarded, if not entirely arrested, by enclosing the reagents in a vessel lined with paraffin wax, although the reaction proceeds rapidly in a vessel having on its walls an adsorbed film of water or a polar compound such as stearic acid.[2]

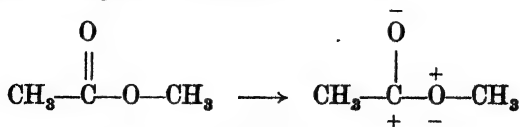
Lowry suggests that organic (non-polar) compounds enter into reaction only by the formation of ions which come into existence by the action of a polar catalyst at the moment when reaction is about to take place. These ions are not supposed to have an independent existence such as the ions have in a salt solution; they are merely in existence for a brief period before being reconverted into neutral molecules.

5. *Hydrolysis and Esterification*

Since the electronic symbols are somewhat confusing in the case of complex structures, it will be convenient to utilize instead the signs + and — attached to the atoms to which polarity is ascribed; but it should be borne in mind that these signs are merely indications of the distributions of the electrons in the systems under review. In this connection it may be well to lay stress once more on the view that when ions adhere to one another there is no real " bond " between them, since they are united by electrostatic attraction and not held together in virtue of a shared duplet of electrons. Thus sodium chloride must be regarded as having the arrangement (I.) and should not be represented by the bonded structure (II.).

$$\text{(I.)}\quad \overset{+}{\text{Na}}\overset{-}{\text{Cl}} \qquad\qquad \text{(II.)}\quad \text{Na—Cl}$$

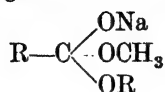
Lowry assumes that under appropriate conditions, the non-polar double bond of the ester radicle may become converted into a polar arrangement, as shown below:

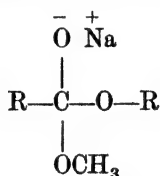
$$CH_3\text{—}\underset{}{\overset{\overset{\displaystyle O}{||}}{C}}\text{—}O\text{—}CH_3 \longrightarrow CH_3\text{—}\underset{+}{\overset{\overset{\displaystyle \overset{-}{O}}{|}}{C}}\text{—}\underset{-}{\overset{+}{O}}\text{—}CH_3$$

The divalent oxygen atom is well known to have residual polar

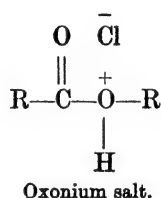
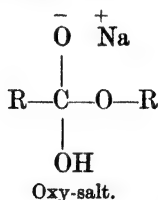
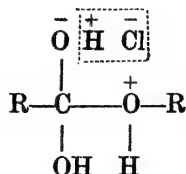
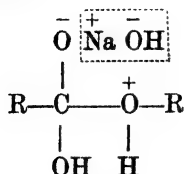
[1] *Ibid.*, 1903, 43, 454.

[2] Norrish, *J.*, 1923, 123, 3006.

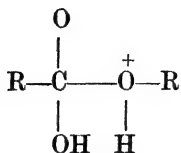
valencies, as was shown by the discovery of the oxonium salts by Collie and Tickle.[1] The polar character of the "opened-up" carbonyl union is suggested by Pechman's observation [2] that sodium methylate forms definite compounds with esters. These compounds are generally given the formula

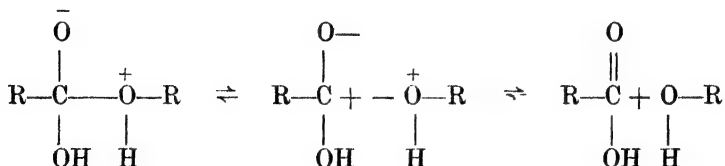
$$R{-}C\begin{cases}ONa\\ OCH_3\\ OR\end{cases}$$

but Lowry prefers to regard then as salts formed by the attraction of ions and not as completely bonded structures :

$$\begin{array}{c}\overset{-}{O}\ \overset{+}{Na}\\ |\\ R{-}C{-}O{-}R\\ |\\ OCH_3\end{array}$$

Applying these ideas to the case of the hydrolysis of an ester by means of an alkali or an acid, Lowry points out that the initial reaction-product may be regarded as either an oxy-salt or an oxonium salt :

Oxy-salt. Oxonium salt.

Since hydrolysis usually takes place in presence of excess of water, Lowry assumes that this water also plays a part in the ionic process, and that whilst a molecule of acid or alkali attacks one new polar grouping in the ester molecule, a water-molecule attaches itself to the other. The resulting structures can be written thus :

[1] Collie and Tickle, *J.*, 1899, **75**, 710. [2] Pechman, *Ber.*, 1898, **31**, 503.

and the skeleton common to both is obviously :

$$\begin{array}{lll} & O & \\ & | & \\ R- & C- & \overset{+}{O}-R \\ & | & | \\ & OH & H \end{array}$$

Thus by utilizing the salt-forming properties of a bi-polar molecule, Lowry's hypothesis suggests how three important things can be achieved : (1) the addition of a molecule of water to the ester without immediate disruption ; (2) the production of a molecule of acid and one of the alcohol with all the atoms held together by real bonds and attached to one another only by a superfluous non-polar bond ; (3) the final rupture of this last bond by an ionization which will reconstitute a polar oxygen atom on the one hand and a non-polar double bond on the other, thus

$$\begin{array}{lll} & \bar{O} & \\ & | & \\ R- & C- & \overset{+}{O}-R \\ & | & | \\ & OH & H \end{array} \rightleftharpoons \begin{array}{llll} & O- & & \\ & | & & \\ R- & C & + & -\overset{+}{O}-R \\ & | & & | \\ & OH & & H \end{array} \rightleftharpoons \begin{array}{llll} & O & & \\ & \| & & \\ R- & C & + & O-R \\ & | & & | \\ & OH & & H \end{array}$$

It is usually assumed that esterification and hydrolysis are converse processes ; but it must be remembered that this statement is true only with limitations. Acids can act as catalysts in both hydrolysis and esterification ; but bases do not assist esterification though they have a marked effect in hydrolysis reactions.

According to Lowry, the following inferences can be drawn with regard to the mechanism of esterification. In the first place, acids act in virtue of their ability to supply protons which are added to the molecules catalysed, thus forming unstable addition-compounds which subsequently yield the final products. These addition-compounds are not derived from the acids undergoing esterification but are oxonium derivatives of the alcohols produced by the addition of a proton to the alcoholic molecule. On the foregoing basis, Lowry represents the esterification process as taking place in the following stages :—

$$R—C(OH):O \;+\; \overset{+}{H}O\langle{}^{H}_{R}$$

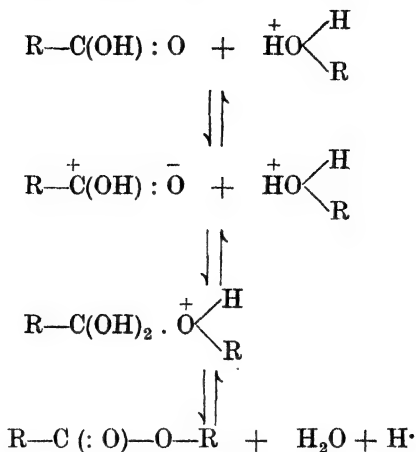
$$\rightleftharpoons$$

$$R—\overset{+}{C}(OH):\overset{-}{O} \;+\; \overset{+}{H}O\langle{}^{H}_{R}$$

$$\rightleftharpoons$$

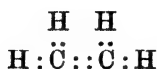
$$R—C(OH)_2\,.\,\overset{+}{O}\langle{}^{H}_{R}$$

$$\rightleftharpoons$$

$$R—C\,(:O)—O—R \;+\; H_2O + H^{\cdot}$$

6. *Isomeric Change*

It has been pointed out by Lowry [1] that three distinct types of intramolecular change can be recognized.* In the first type the change consists in a movement of one or more electrons to fresh situations in the molecule. This Lowry indicates by the term *electrotropy.* The second type of intramolecular change is brought about by the wandering of protons and has been named by him *prototropy.* Finally, when complex radicles move from one position to another within the structure, Lowry distinguishes the case as one of *ionotropy.* A brief examination of the various types will bring to light some points of interest.

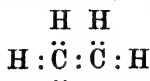
(*a*) *Electrotropy.*—Lowry regards electrotropy as the principal factor in the activation which he assumes as a frequent prelude to chemical change, especially among the carbon compounds. For example, ethylene can be represented on the Lewis symbolism by

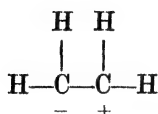
$$\begin{matrix} & H & & H & \\ H: & \ddot{C} & :: & \ddot{C} & :H \end{matrix}$$

wherein four electrons are shared between the two carbon

[1] Lowry, *Lecture to the Institut International Solvay* (1925).

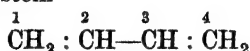
* It should be noted that Lowry expressly refrains from including *all* types of isomeric change in these three categories.

systems. If one duplet now passes completely into the system of one of the carbon systems, the symbol becomes

$$\begin{array}{ccccccc} & & H & & H & & \\ H & : & \overset{\cdot\cdot}{\underset{\cdot\cdot}{C}} & : & \overset{\cdot\cdot}{C} & : & H \end{array}$$

wherein the left-hand carbon system is now negatively charged whilst the right-hand system has an equal and opposite positive charge:

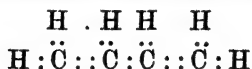
$$\begin{array}{ccccc} & H & & H & \\ & | & & | & \\ H— & C & — & C & —H \\ & - & & + & \end{array}$$

Electrotropy, then, may be the means of producing polarity in a molecule, or, conversely, a polar molecule may be reduced to an electrically neutral condition by electrotropic change. Owing to electronic mobility, it seems impossible in practice to isolate two electrotropic isomers from one another; and Lowry regards it as possible that one electrotrope is a mere phase in the process of reaction.

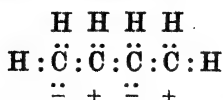
The most interesting case in which the idea of electrotropy can be applied is that presented by Thiele's theory of partial valencies. In the system

$$\overset{1}{C}H_2 : \overset{2}{C}H—\overset{3}{C}H : \overset{4}{C}H_2$$

the points attacked by a bromine molecule are the carbon atoms marked 1 and 4, and a new double bond is formed in the centre of the molecule; so that the final product is

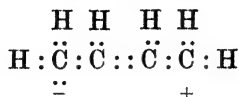
$$CH_2Br—CH : CH—CH_2Br$$

This can be illustrated by using Lewis's symbolism as follows. In the first place, the electrons are distributed thus:

$$\begin{array}{ccccccccc} & & H & . & H & & H & & H \\ H & : & \overset{\cdot\cdot}{C} & :: & \overset{\cdot\cdot}{C} & : & \overset{\cdot\cdot}{C} & :: & \overset{\cdot\cdot}{C} : H \end{array}$$

Now let an electrotropic change be assumed whereby two duplets of electrons become absorbed into two of the carbon systems, thus producing a phase of ionization:

$$\begin{array}{ccccccccccc} & & H & & H & & H & & H & & \\ H & : & \overset{\cdot\cdot}{C} & : & \overset{\cdot\cdot}{C} & : & \overset{\cdot\cdot}{C} & : & \overset{\cdot\cdot}{C} & : & H \\ & & \overset{\cdot\cdot}{-} & & + & & \overset{\cdot\cdot}{-} & & + & & \end{array}$$

This arrangement would obviously not concord with the results of experiment, since an ionized bromine molecule would be free

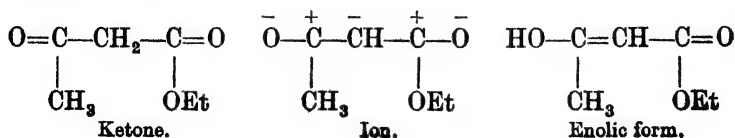
to attack any pair of oppositely-charged carbon atoms. It is therefore necessary to postulate a second electrotropic change wherein the duplet of electrons attached to the third carbon atom of the chain becomes shared with the second atom :

$$\begin{array}{ccccccccccc} & & H & & H & & H & & H & & \\ & & \cdot\cdot & & \cdot\cdot & & \cdot\cdot & & \cdot\cdot & & \\ H & : & C & : & C & :: & C & : & C & : & H \\ & & \cdot\cdot & & & & & & & & \\ & & - & & & & & & + & & \end{array}$$

Inspection of this formula will show that these two movements of the electron duplets have (*a*) produced opposite charges on the terminal carbon atoms, and (*b*) constituted a fresh double bond in the centre of the molecule while leaving this new ethylenic linkage devoid of polarity. In fact, the electrotropic rearrangements have given rise to a structure which would react just as the hydrocarbon does behave in practice.

(*b*) *Prototropy.*—This depends on the migration of a proton from one point to another within the molecule, usually with a consequent rearrangement of the bond-forming electrons. Since prototropy entails the shifting of an actual material particle, it is possible in many cases to isolate both isomeric forms of the compound in a pure state. For example, the enolic and ketonic varieties of acetoacetic ester can be separated from each other ; and the normal and *aci*-forms of some pseudo-acids have been obtained.

The process of prototropy, when considered from the electronic standpoint, obviously is a somewhat complex one. In the first place, the removal of a proton from the molecule necessarily leaves a negative ion in existence. Further, since the proton re-attaches itself at a fresh point in the molecule, there must be a negative charge at this spot, as well as at the point of detachment. To put the matter in other words, prototropy involves : (*a*) the detachment of the proton ; (*b*) the formation of an ion with a double negative charge ; (*c*) the re-attachment of the proton ; and (*d*) the restoration of non-polarity. In the case of acetoacetic ester, the three structures involved are evidently those shown below :

$$\begin{array}{ccccc} O{=} & C & —CH_2— & C & {=}O \\ & | & & | & \\ & CH_3 & & OEt & \end{array} \qquad \begin{array}{ccccc} \overset{-}{O}— & \overset{+}{C} & —\overset{-}{C}H— & \overset{+}{C} & —\overset{-}{O} \\ & | & & | & \\ & CH_3 & & OEt & \end{array} \qquad \begin{array}{ccccc} HO— & C & {=}CH— & C & {=}O \\ & | & & | & \\ & CH_3 & & OEt & \end{array}$$

Ketone. **Ion.** **Enolic form.**

Further light is thrown on the problem when it is recalled that the interconversion of these two prototropic forms can be arrested by working under "acatalytic" conditions.[1] This obviously implies that prototropic change is facilitated (if not actually produced) by some external mechanism; and further support is gained for this view when it is remembered that the mutarotation of nitro-camphor—due to another prototropic change—is arrested by working in inert solvents.[2]

A catalyst may be supposed to influence prototropic change in either of two ways: for it may (1) facilitate the withdrawal of the proton from the parent molecule or (2) promote the addition of the proton to the ion. In the prototropic changes mentioned above, the most efficient catalysts are bases; acids are less effective; and water is still less so. Lowry regards bases as being chiefly effective as proton-removers; whilst acids act as facilitators of the re-insertion of the proton. Water, being amphoteric, can act in both ways; but its low ionization makes it a poor agent in these particular cases. It should be remembered, however, that the efficiency of a base as a proton-remover is also a measure of its activity in preventing the return of the proton to the organic ion. Conversely, though an acid is a good agent for the insertion of protons, it tends to repress the ionization which yields the free proton. The presence of water, owing to its amphoteric character, will facilitate the catalysis of prototropic change by either bases or acids.[3]

Lowry [4] has shown how his electronic views of prototropic change can be applied in order to account for the phenomena of optical inversion, mutarotation, and the Walden Inversion; but space does not permit an examination of these subjects here, and the reader is referred to the original papers for further information.

Ionotropy.—Having now considered the possible results of the shifting of electrons and simple protons within a molecule, it is necessary to turn to a series of phenomena which cannot be explained on the basis of either of these changes. At first

[1] K. Meyer, *Ber.*, 1920, **53**, 1410.

[2] Lowry, *J.*, 1899, **75**, 211; 1908, **93**, 119; 1925, **127**, 1371; compare Purdie and Irvine, *J.*, 1904, **85**, 1049.

[3] Compare O'Sullivan and Thomson, *J.*, 1890, **57**, 869; Lowry, *J.*, 1925, **127**, 1371; Lowry and Richards, *ibid.*, 1385.

[4] Lowry, *Lecture to the Institut International Solvay*, 1925; *J.*, 1925, **127** 371; Lowry and Richards, *ibid.*, 1385.

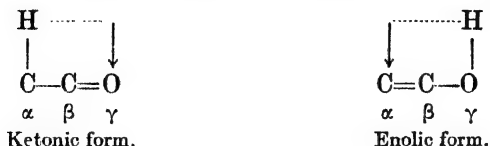
sight it might seem, as Lowry points out, that isomeric change may be due entirely to an intramolecular turmoil caused by thermal agitation, after which the atoms settle down into a structure different from that existing before heat was applied. There is a limiting factor here which cannot be neglected. In some cases the thermal agitation sufficient to produce isomeric change may be more than sufficient to disrupt the molecular structure completely; and thus any effort to bring about an intramolecular rearrangement by purely thermal means may result in the collapse of the molecular structure into simpler units. For example, if an attempt is made to interchange the hydrogen atom and hydroxyl group in the radicle —CH . OH— in the sugar series, the temperature may be raised to a degree at which the sugar molecule loses water and yet up to that stage no inversion of the secondary alcoholic grouping is observed. It appears, in fact, that in cases such as these the "disruption-temperature" is lower than any possible "rearrangement-temperature."

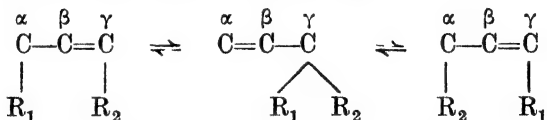
Thermal agitation alone, then, may prove insufficient to bring about isomeric change; and since many intramolecular rearrangements are facilitated by the presence of catalysts, Lowry prefers the hypothesis of a mechanism akin to that suggested by him in connection with prototropic change. He proposes, in fact, to regard a number of isomeric changes as due to the wandering within the molecule of atomic groups having the character of ions.

Lapworth,[1] as far back as 1901, suggested that "it is to electrolytic dissociation, often doubtless in extremely minute amount, that the majority of changes in organic compounds may be most probably assigned." In the case of isomeric change, this means that an atom, or group of atoms, is detached from the molecule in the form of an ion, and that thereafter it migrates to a fresh point of attachment elsewhere in the structure. Lapworth [2] had previously shown that a large number of these group-migrations were subject to simple rules which may be summarized here. In the first place, Lapworth laid down that in desmotropic compounds the labile group moves from an α-atom to attach itself to the γ-atom, the suitable rearrangement of the linking taking place between the three fixed atoms, α, β, and γ.

[1] **Lapworth, *J.*, 1901, 79, 1266.** [2] ***Ibid.*, 1898, 73, 445.**

$$\begin{array}{ccc} H & \cdots\cdots & \downarrow \\ | & & \\ C{-}C{=}O \\ \alpha \;\; \beta \;\; \gamma \end{array} \qquad\qquad \begin{array}{ccc} \downarrow & \cdots\cdots & H \\ & & | \\ C{=}C{-}O \\ \alpha \;\; \beta \;\; \gamma \end{array}$$

Ketonic form. Enolic form.

Further, two mobile groups attached to the atoms α and γ may change places without any final alteration of the original disposition of the single and ethylenic linkages; for if a group on the α atom moves to the γ atom and in so doing produces a certain rearrangement of the bonds, this arrangement will be reversed again by the passage of a group on the γ atom to the α atom, and thus the original bond-grouping will be restored as a result of the interchange of the groups.

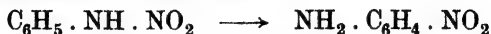
$$\begin{array}{c} \alpha \;\; \beta \;\; \gamma \\ C{-}C{=}C \\ | \qquad\; | \\ R_1 \qquad R_2 \end{array} \rightleftharpoons \begin{array}{c} \alpha \;\; \beta \;\; \gamma \\ C{=}C{-}C \\ \diagup \diagdown \\ R_1 \;\; R_2 \end{array} \rightleftharpoons \begin{array}{c} \alpha \;\; \beta \;\; \gamma \\ C{-}C{=}C \\ | \qquad\; | \\ R_2 \qquad R_1 \end{array}$$

Finally, a labile group may move along a chain of alternately singly and double bound atoms, the ethylenic and single linkages changing places in the path of the labile group so that this group may travel from the α to the γ and then on to the ε position in the chain.

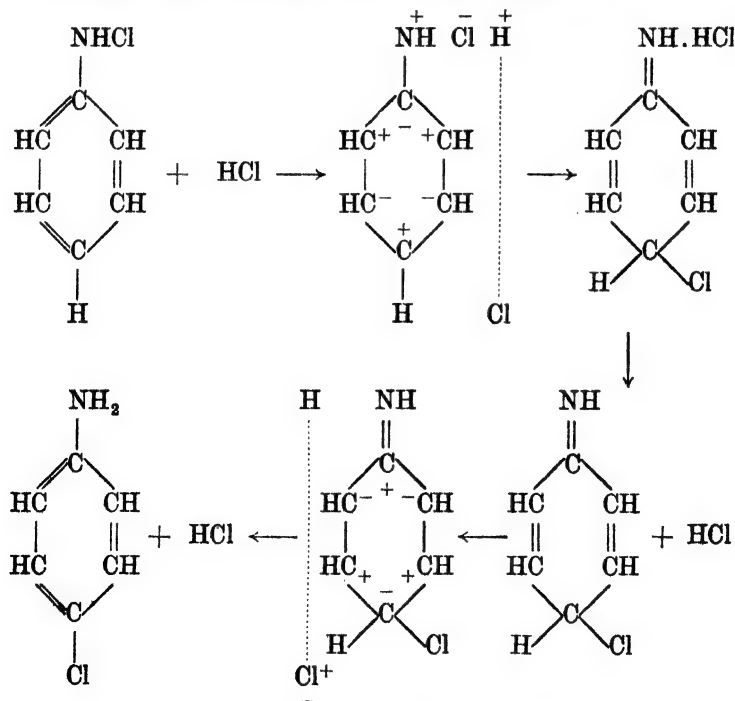
Now, as Lowry points out, the αγ-rule of Lapworth can be very simply explained by using the conception of polar molecules and multipolar ions which has been discussed in an earlier section of this chapter,[1] since in such rearrangements, positive and negative charges may alternate on the atoms of the chain. In order to cover the whole ground, however, it is necessary to go more closely into the question of the mechanism whereby these ionotropic changes may be brought about.

Though at first sight there appears to be a marked resemblance between prototropic and ionotropic changes, since both types may be regarded as ionic transferences, there is a striking difference between the two sets of phenomena. Speaking generally, prototropic changes are promoted most effectively by basic catalysts and less efficiently by acidic catalysts; whereas in sharp distinction to this it is found that ionotropic changes are promoted only by acidic catalysts and are actually arrested

[1] Compare Lowry, *J.*, 1923, **123**, 822; *Bull. Soc. chim.*, 1924 (4), **35**, 815, 905.

in neutral or alkaline media. For example, phenyl-chloroamine, $C_6H_5 . NH . Cl$, is stable in presence of alkalis; and whenever the conditions are favourable to its conversion into chloro-aniline, $NH_2 . C_6H_4 . Cl$, hydrochloric acid can be detected in the solution.[1] Similar phenonema were observed in the isomeric change of nitro-amines into nitranilines :

$$C_6H_5 . NH . NO_2 \longrightarrow NH_2 . C_6H_4 . NO_2$$

Lowry infers from these results that the active catalyst for the interchange of the radicles H and X between side-chain and nucleus is generally the acid HX.

As an illustration of Lowry's views on the catalytic mechanism, the conversion of phenyl-chloroamine into *p*-chloraniline by means of hydrochloric acid may be selected. It should be noted that the signs + and — are here used to indicate real electrical charges and do not represent anything in the nature of the vaguer "polarities" which are often symbolized in this way.

¹ Orton, *Brit. Assoc. Reports*, **1908**, 115; **1909**, 147.

Lowry suggests that the readiness with which chemical changes (especially isomeric changes) involving distant atoms take place in aromatic compounds may be attributed to the manner in which conjugated systems can convey electric charges from one end of the system to the other without any simultaneous migration of the intermediate atoms: a process akin rather to metallic conduction than to ionic conduction.[1]

7. *Chelate Compounds*

Acetoacetic ester gives rise to two isomeric ethyl derivatives: ethyl-acetoacetic ester (I.) and ethyl-β-ethoxycrotonate (II.).

$$\underset{\text{(I.)}}{} \quad CH_3—CO—\underset{\displaystyle Et}{\underset{|}{CH}}—COOEt \qquad\qquad CH_3—\underset{\displaystyle OEt}{\underset{|}{C}}{=}CH—COOEt \quad \underset{\text{(II.)}}{}$$

the first being derived from the ketonic and the second from the enolic form of the parent substance. An examination of the absorption spectra of these compounds by Baly and Desch [2] showed that none of them contained an absorption band. This proved that neither the ketonic nor the enolic structure in the acetoacetic ester molecule is in itself capable of exerting selective absorption.

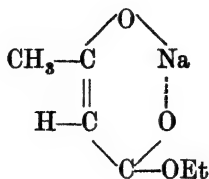
But when some sodium hydroxide is added to the solution of acetoacetic ester, a deep absorption band appears in the spectrum in the region of oscillation frequency 3700; and this band increases in its penetration with the addition of more and more alkali. A similar band was observed in the spectrum of the aluminium derivative of acetoacetic ester.

Since an ordinary specimen of acetoacetic ester is a mixture of the keto and enol forms, and since its spectrum shows no absorption band, it is clear that neither of these structures produces this banded absorption. Baly and Desch surmised that the origin of the band was "due to the dynamic isomerism between the two forms," so that the band arose when one isomer changed over into the other. They further assumed that the isomeric change was catalyzed by the presence of alkali and

[1] Compare Lowry, *Nature*, 1925, **115**, 376.
[2] Baly and Desch, *J.*, 1904, **85**, 1029.

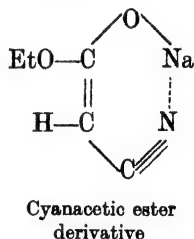
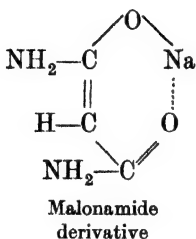
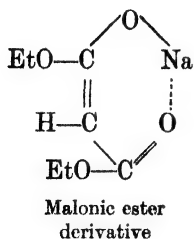
retarded by the addition of acid, as they found that the banded absorption diminished when acid was added to the solution. This led them to the further speculation [1] that the labile atom was " in a state of incipient dissociation, and may thus be looked upon as a potential ion." It was later shown by Knorr [2] that both acids and bases have the same influence upon the transformation of the enolic into the ketonic form ; which proves the untenability of the foregoing hypothesis.

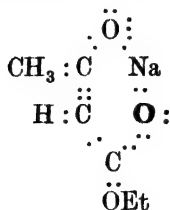
A more satisfactory suggestion was put forward by Hantzsch [3] as the result of further investigation. According to him, the absorption band was due to the presence of the sodium derivative of acetoacetic ester, and had nothing to do with isodynamic change. The deepening of the band on the addition of more and more alkali was merely an illustration of the Mass Action Law, since the presence of the additional alkali tends to restrict the hydrolysis of the acetoacetic ester sodium derivative. On this basis, the addition of extra alkali tends to increase the percentage of sodium derivative in the solution ; and as the band is due to the presence of the sodium derivative, it becomes more marked as more of the sodium derivative is produced.

This interpretation appears to be the correct one ; but it obviously raises a fresh difficulty. The sodium salts of ordinary fatty acids such as sodium acetate, do not show selective absorption. There are no bands in the absorption spectra of their solutions. Thus, if Hantzsch's view be a sound one, there must be some profound difference between the sodium derivative of acetoacetic ester on the one hand, and an ordinary sodium salt on the other. Hantzsch suggested that the sodium derivative was an " internal complex salt " according to the ideas of Werner, which were then current. He formulated the structure thus :

[1] Baly and Desch, *J.*, 1905, **87**, 767.
[2] Knorr, *Ber.*, 1911, **44**, 1150.
[3] Hantzsch, *Ber.*, 1910, **43**, 3049.

where the sodium was supposed to be attached to the carbonyl oxygen by an "auxiliary valency," which is indicated by the dotted line. As no such grouping can exist in the ordinary sodium salts of the simple fatty acids—since they have no carbonyl group in the chain—this hypothesis of Hantzsch fitted the facts.

It will be seen that in the above formula the carbonyl atom and the sodium atom are in the 1,6-position with regard to each other and are thus spatially adjacent. This feature is important, as it has been shown [1] that the sodium derivative of urethane, Na . NH . COOEt, has no band in its spectrum; and inspection of its formula shows that the sodium atom and the carbonyl oxygen atom are in the 1,4-position and therefore are not adjacent in space. On the other hand, an absorption band in the region of frequency 3700 is found in the spectra of alkaline solutions of the following substances: malonic [2] ester, $CH_2(COOEt)_2$; methyl-malonic ester,[2] $CH_3 . CH(COOEt)_2$; malonic methyl ester, $CH_2(COOMe)_2$; malonamide, $CH_2(CO . NH_2)_2$; cyan-acetic ester, $CN . CH_2 . COOEt$. In each of these cases, a six-membered ring is possible, assuming that the sodium derivative is derived from an enolic form; and it will be seen that in some cases a nitrogen atom can play the same part as the oxygen atom of the carbonyl group in the ring derived from acetoacetic ester:

Malonic ester derivative | Malonamide derivative | Cyanacetic ester derivative

G. N. Lewis's electronic theory of valency has made it possible to give a more definite representation of the matter.[3] On that basis, the electronic arrangement in the case of the sodium derivative of acetoacetic ester can be illustrated thus:

[1] Brannigan, Macbeth and Stewart, *J.*, 1913, **103**, 406.
[2] Macbeth and Stewart, *Proc. Chem. Soc.*, 1913, **29**, 11.
[3] Sidgwick, *Nature*, 1923, 112, 179; Sidgwick, *The Covalent Link in Chemistry* (1933).

Here the carbonyl oxygen of the carboxyl group (printed for clarity in heavy type) donates two electrons to the sodium system, which is also connected to the oxygen of the true carbonyl group (uppermost in the formula) by a normal electron-pair, one member of which is contributed by the oxygen and one by the sodium. The sodium system is thus held tightly by two "claws," as a crab holds its prey in its pincers; and on this account substances of the foregoing type are termed *chelate compounds* from χηλή = a claw.

As regards acetoacetic ester itself, Sidgwick [1] has pointed out that if its enol form had a chelate structure like that of the sodium derivative, it would have no true hydroxyl group in its formula. It should not be associated; its solubility should be less in water and greater in non-polar solvents than the solubility of the keto-isomeride; and it should boil at a lower temperature than the ketonic form. In practice it does show this behaviour.[2]

One or two well-known facts about the solubilities of some metallic derivatives may be mentioned here. The sodium derivative of acetoacetic ester, if anhydrous, is soluble in ether; whereas the hydrated form (containing one molecule of water) is insoluble. The copper derivative is soluble in benzene. The calcium derivative of malonic ester is not very soluble in water or ether; but it is easily soluble in alcohol. The aluminium derivative of malonic ester is soluble in ether, benzene, and ligroin. The copper derivative of acetylacetone is soluble in chloroform. This, obviously, indicates a considerable difference between these substances and simple salts of the fatty series. Again, the aluminium and beryllium derivatives of acetylacetone distil unaltered, which is different from the behaviour of ordinary fatty acid salts.

[1] Sidgwick, *J.*, 1925, 127, 907.
[2] Meyer and Schöller, *Ber.*, 1920, 53, 1410.

8. *Conclusion*

In the foregoing pages only a few examples were selected out of the host of interesting results which have flowed from G. N. Lewis's electronic views of chemical affinity; but sufficient has been said to illustrate the simplification which has followed upon the adoption of his ideas of the octet and the electron-pair as the two keys to structural chemistry. Before leaving the subject, it may be well to point out that we are not without experimental evidence tending to show that Lewis's ideas are something more than mere convenient hypotheses.

As has already been indicated, two distinct types of chemical union can be recognized. In the first place, there is the normal non-polar bond which serves us so well in all the non-ionogenic compounds of carbon; and, secondly, we have the polar type of attraction which is found uniting the ions of bases, acids, and salts. It requires little consideration to see how different in quality are these two modes of linkage.

Let us take up first the case of the non-polar bond. Our experience in organic chemistry is sufficient to convince us that this type of union leads to the formation of very stable skeletons. Rigid structures can be built up which resist all but the most intense efforts to disintegrate them. Further, as the phenomena of stereoisomerism show, these non-polar bonds act as struts in the molecular architecture and brace the whole structure so that casual deformation seems of rare occurrence.

In complete contrast with this are the polar bonds which unite the ions. In them, the attractive forces are so weak that often simple fusion of the material is sufficient to rupture the polar bonds and liberate the ions; and dissolution in ionizing solvents is enough to split ion from ion. Again, except in the crystalline condition, the ionic bond has no power to form rigid structures. In the liquid state, or in solution, the ions behave simply like charged spheres which are capable of rolling at random and the system is devoid of any specific arrangement.

The new methods of crystal analysis by means of X-rays have thrown a flood of light upon the differences between the

two types of chemical affinity. It has been shown that when the non-polar bonds of chemical structure are present, the crystal is built up from atoms; whereas crystals of metallic salts

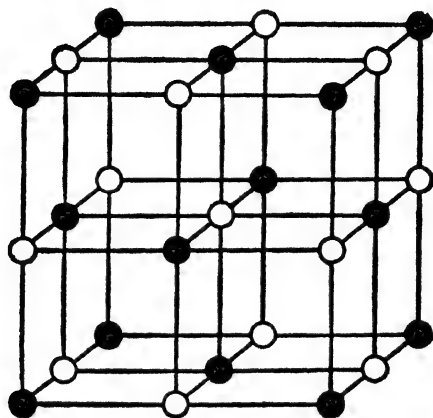



Fig. 3

have been proved to be composed of ions as units. Not only so, but the ions are arranged simply as though they were an assemblage of close-packed spheres. For example, Fig. 3 shows the grouping of part of a sodium chloride crystal.

Here the white circles represent sodium ions, whilst the dark circles indicate chlorine ions. Obviously each sodium ion is surrounded, in such a crystal, by six chlorine ions which are symmetrically placed about it in space; and similarly each chlorine ion has six sodium ions arranged symmetrically in space around it. This is the grouping which might be expected from a simple close-packing of mutually-attracting spheres. There is no sign of any " directed " bonds such as the van't Hoff-Le Bel theory demands in the case of carbon compounds; and the ions are so placed that the spaces between them are reduced to a minimum.

When we turn to the diamond crystal, wherein the bonds are non-polar in character, a completely different picture is seen. Here the arrangement in space is such that each carbon atom lies at the centre of gravity of a tetrahedron formed by its four nearest neighbours; and the arrangement can also be regarded as being built up from groups of rings with six carbon atoms

in each ring. In fact the model can be constructed quite easily from the ordinary models used to illustrate stereochemical questions (see Fig. 4).

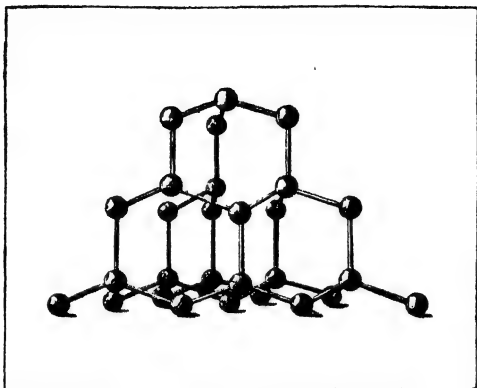



Fig. 4

Inspection of Fig. 4 will show that instead of the close-packing arrangement of sodium chloride, we have here an open lattice-work in which a great proportion of the total space is necessarily empty. In point of fact, if these open interstices in the crystal did not exist, the diamond would have a density of 8 instead of the actual density of 3·5.

It is thus clear from the evidence of X-ray analysis that the polar and non-polar bonds are different in the groupings which they produce. It may be inferred that polar affinity is evenly distributed over the whole surface of the ion; that it acts uniformly in all directions if necessary; and that it is capable of subdivision even in the case of monovalent ions. The non-polar affinity, on the other hand, acts in specific strength in specific directions.

CHAPTER XVII

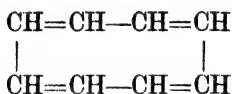
SOME UNSOLVED PROBLEMS

In the foregoing pages many examples have been given to illustrate the surmounting of difficulties, either practical or in theory, which at first sight appeared insuperable; and a study of the countless successes which have been achieved by organic chemists in the solution of the problems of chemical constitution cannot fail to raise sanguine hopes that in the future the most complicated structures will be elucidated. Yet it must be freely admitted that even the simplest compounds and reactions remain fruitful fields for further investigation; for it is precisely in this region that modern organic chemistry is most backward. Whilst the frontier of the subject is being pushed ever onward, the older branches remain very much where the pioneers left them; and our knowledge of fundamental things has not increased at anything like the same rate as our other acquirements. In the present chapter, an attempt will be made to direct attention to a few of the main points which might repay further thought and experiment.

The greatest problem before organic chemists at the present day is the application of modern electronic views to the salient phenomena among the reactions of the carbon compounds. The peculiarities of benzene, the extraordinary variety of effects observed in the rupture of double bonds, and especially the influence of conjugation, are examples of fields which seem to offer outlets for a considerable amount of speculation in connection with G. N. Lewis's theory. Since it must be admitted that all octets are not equally stable, a promising line of attack seems likely to be found in correlating the octet theory with the results now included under the head of Michael's Distribution Principle. Not quite so tempting, though yet of considerable

interest, is the problem of cyclic groupings and their influence on physical properties such as refractive index. And here, too, the phenomena of spatial conjugation seem to deserve mention.

In the group of cyclic compounds, an unexplained phenomenon meets us at once: the benzenoid character possessed by certain substances. This peculiar series of properties is evidently not produced by one factor alone, but must be the result of at least three coexisting influences. The alternating system of double and single bonds which is characteristic of the benzene system is to be found in other molecules as well. It occurs, for example, in hexatriene: $CH_2 : CH . CH : CH . CH : CH_2$; but no aromatic character is shown by this substance. Again, the mere occurrence of a six-membered ring in a compound confers no benzenoid characteristics on the substance, as is seen in the case of the terpenes or the hexamethylene derivatives. Finally, even the combination of a ring and the alternate grouping of single and double bonds does not suffice to produce aromatic properties, since both such characteristics are present in cyclo-octatetraene:

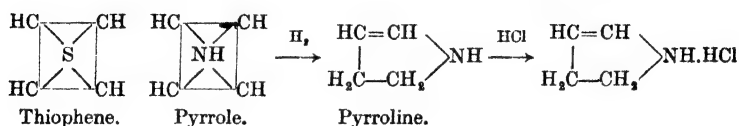
$$\begin{array}{l} CH{=}CH{-}CH{=}CH \\ | \qquad\qquad\qquad\quad | \\ CH{=}CH{-}CH{=}CH \end{array}$$

and yet this substance [1] is not benzenoid in character. It is thus evident that the *number* of the carbon atoms in the ring must have some influence; and that to possess the aromatic characteristics a compound must contain: (1) a cyclic structure; (2) six atoms in the ring; * (3) a symmetrical arrangement of alternate double and single bonds within the ring. Why this particular arrangement should be required and why it and only it can confer aromatic properties upon a hydrocarbon molecule is a point upon which speculation has hitherto failed to throw light. The most plausible solution is to be found in Collie's benzene space-formula; [2] but even it leaves room for further thought on the subject.

[1] Willstätter and Waser, *Ber.*, 1911, **44**, 3423.

* It should be noted that in such substances as pyridine, atoms other than carbon ones can form part of the ring and still the benzenoid character is maintained to a great extent.

[2] Collie, *J.*, 1897, **71**, 1013.

The resemblance to the benzene characteristics which is exhibited by thiophene is another point upon which no satisfactory views have been expressed. It may be recalled that although the usual formulae for thiophene and pyrrole contain atoms capable of forming " onium " derivatives by the addition of alkyl iodides, no such addition reaction has been observed in either case. If, however, pyrrole be reduced to dihydro-pyrrole, the nitrogen atom apparently becomes normal in this respect; and ammonium salt formation takes place. This behaviour could be expressed by means of the following formulae :—

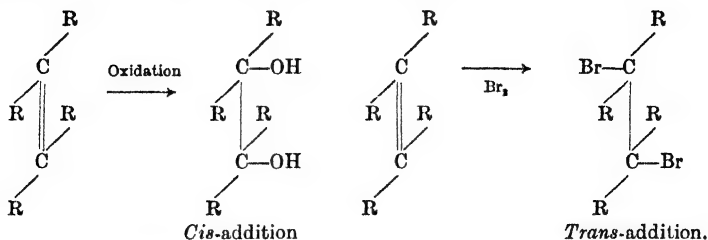
```
HC───CH   HC───CH    H₂   HC=CH             HCl   HC=CH
 |╲ ╱|     |╲ ╱|    ──→    |     >NH       ──→     |     >NH.HCl
 | S |     | NH|          H₂C—CH₂                 H₂C—CH₂
 |╱ ╲|     |╱ ╲|
HC───CH   HC───CH
Thiophene. Pyrrole.       Pyrroline.
```

but in view of other reactions it seems doubtful if this view can be maintained.

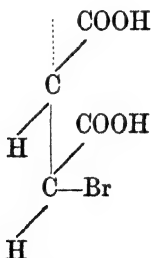
In the field of optical activity, a most surprising result has been recorded by McKenzie.[1] On crystallizing potassium hydrogen racemate from a solution of *l*-malic acid, he obtained a crop of dextro-rotatory crystals consisting of potassium hydrogen racemate with a small admixture of potassium hydrogen *d*-tartrate. Similar results were observed on adding *l*-malic acid to solutions of potassium or sodium racemate. Fifteen other optically active acids were tried; but none gave the same positive result as malic acid. It may be frankly admitted that these phenomena cannot be explained on the basis of our present ideas about ions and asymmetry; and further investigations in the field must be awaited before the problem can be cleared up.

Another field of inquiry is opened up by the discovery that oxidizing agents and halogen molecules appear to act in entirely different ways upon unsaturated linkages.[2] The oxidizing agent attacks a single " side " of the molecule, whereas the halogen atoms attach themselves in the *trans*-position as shown below :—

[1] McKenzie, *J.*, 1915, **107**, 440; McKenzie and Walker, *J.*, 1922, **121** 349; McKenzie, Plenderleith, and Walker, *J.*, 1923, **123**, 2875.

[2] Michael, *J. Amer. Chem. Soc.*, 1918, **40**, 704, 1674.

Cis-addition *Trans*-addition.

Frankland [1] has suggested that this may be due to the atoms in a halogen molecule being separated by a distance sufficient to bring them on opposite sides of the ethylenic molecule when they react with it. Stewart [2] ascribes the phenomenon to a non-simultaneity in the addition-reaction in the case of the two carbons united by the ethylenic linkage. Thus if one carbon atom is attacked before the other, there will momentarily be formed the grouping :

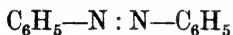
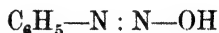
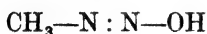
COOH
C
H COOH
C—Br
H

and the final situation of the second bromine will be determined by the directive forces which this complex exerts upon the entering atom. In Stewart's view, these forces tend to drive the incoming atom into the *trans*-position. The phenomenon is to some extent akin to that of the Walden Inversion.

Other examples of analogous " directing " agencies are to be found in the phenomena of benzene substitution and in the field of stereochemistry. Thus in the esterification of an active acid with an alcohol it is found that the rate of reaction between the *d*-acid and the *d*-alcohol is different from that of the reaction between the *d*-acid and the *l*-alcohol ; similar results are observed in the breakdown of active materials by means of active catalytic agents ; and the influence of directive factors in asymmetric syntheses is obvious. Up to the present, there is no " explanation " of these things.

[1] Frankland, *J.*, 1912, **101**, 673. [2] Stewart, *Stereochemistry*, 1919, p. 118.

In a similar class we may place those cases wherein the same reagent acts differently upon molecular structures which we symbolize by identical signs. For example, we write the same symbol for a double bond whether it be present in an ethylenic linkage, a carbonyl radicle, or a carbon-nitrogen union; yet these three types differ entirely from each other in their behaviour towards hydrogen and bromine. It may be objected that although the bonds are written in the same way, we mentally interpret them differently according to the atoms which they join; but as we have already seen,* even the ordinary ethylenic bond is used to cover a number of cases wherein the reactions of the compounds are not even remotely alike.

Molecular stability is another problem of which barely the fringe has been surveyed. Why is the compound (I.) extremely stable while (II.) is unstable and (III.) is non-existent under the same experimental conditions?

$$C_6H_5—N:N—C_6H_5 \quad \text{(I.)} \qquad C_6H_5—N:N—OH \quad \text{(II.)}$$

$$CH_3—N:N—OH \quad \text{(III.)} \qquad C_6H_5—P:P—OH \quad \text{(IV.)}$$

No satisfactory theory of this apparently simple problem has yet been suggested, nor have we any hypothesis which accounts for the non-isolation of the phosphorus analogue (IV.) of diazobenzene hydrate.

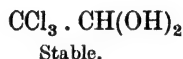
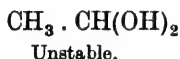
Again, carbonic acid is unstable; but when a sodium atom is substituted for one of the hydrogen atoms, the sodium bicarbonate so formed is fairly stable. The same rule holds good in the cases of sulphurous acid and sodium bisulphite. A plausible explanation may be found in the fact that intramolecular elimination of water is possible in the case of the acids, whereas the removal of water from the salts would demand the co-operation of two molecules. A similar explanation would account for the relative stability of benzene sulphonic acid as compared with sulphurous acid; but here another problem presents itself. Why is potassium bisulphite readily oxidized to potassium hydrogen sulphate, whereas it is impossible to prepare a stable compound of the formula $C_6H_5 . SO_4H$ by the oxidation of benzene sulphonic acid?

* See Vol. I., Chapter XVI.

There appears to be some influence at work which prevents the accumulation of certain atomic groups upon one carbon atom. Thus although tetrachloromethane, CCl_4, and tetranitromethane, $C(NO_2)_4$, are compounds which can be distilled without decomposition at ordinary pressure, the analogous tetra-amino-derivative, $C(NH_2)_4$, is unknown; and reactions leading to its formation [1] produce only guanidine $NH : C(NH_2)_2$. In the case of four hydroxyl radicles attached to one carbon atom the decomposition goes even further; the compound $C(OH)_4$ breaks down instantaneously in order to yield carbon dioxide and water.

In a minor degree this instability can be traced in certain other reactions. Chloroform is unaffected by alkali bisulphites, whereas chloropicrin reacts readily to yield trisulphonates such as $H.C(SO_3K)_3$, so that evidently the introduction of the nitro-group has lowered the stability of the compound.

As an offset to this, the stabilizing action of a chlorine substituent may be noted. At ordinary temperatures acetaldehyde forms no stable addition product with water; whereas the hydrate of chloral is comparatively stable:

$CH_3 . CH(OH)_2$	$CCl_3 . CH(OH)_2$
Unstable.	Stable.

It appears that an extension of our knowledge of the stabilizing and unstabilizing influences of various substituents in methane might open up a very interesting line of research.

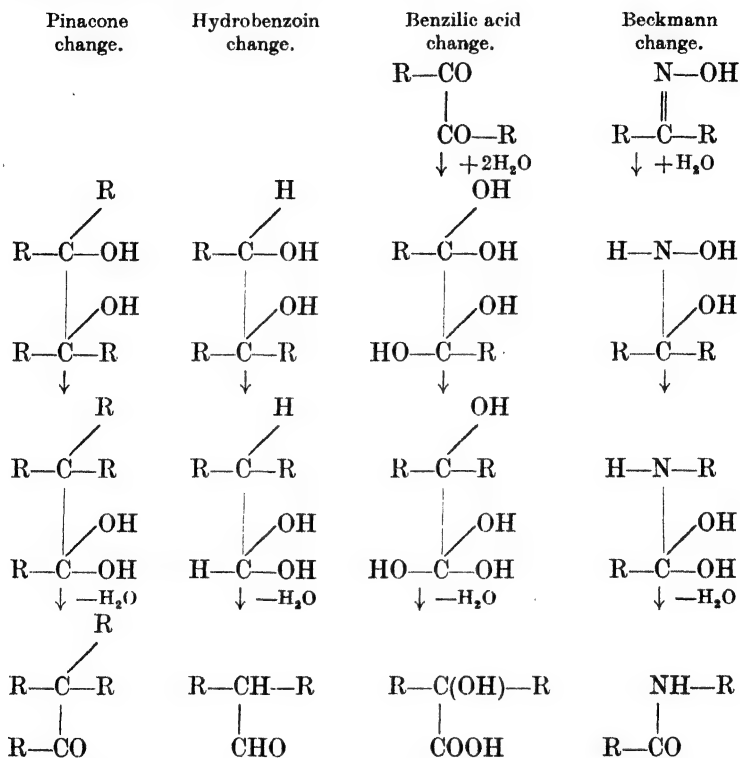
Intramolecular change * furnishes one of the most interesting fields for speculation in organic chemistry. Two problems are evidently involved in the question: for we may inquire, in the first place, why one particular structure is more stable than an isomeric form; or, secondly, we may endeavour to conjecture the mechanism of the process whereby the one isomer is converted into the other. Let us take certain well-known examples of intramolecular changes and see if they can be accounted for by any general principle. It will be sufficient if we examine the pinacone change, the Beckmann rearrangement, the benzilic acid change, and the hydrobenzoin change.

All these four types of rearrangement within the molecule

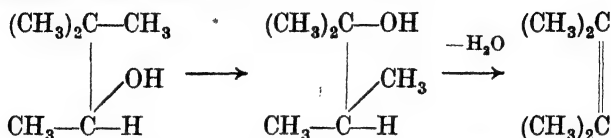
[1] Rakshit, *J. Amer. Chem. Soc.*, 1914, **36**, 1221.

* For some general views on intramolecular change see Lapworth, *J.*, 1898, **73**, 445; Tiffenau, *Revue gen. d. Sciences*, 1907, 583; and Lowry's lecture to the *Institut international de Chimie Solvay*, April, 1925.

can be brought into line if it be assumed that the first stage in the reaction consists of the addition of an outside reagent, which for the sake of simplicity we may regard as water. The changes would then be expressible as shown below ; and the parallelism between them is obvious at a glance :—

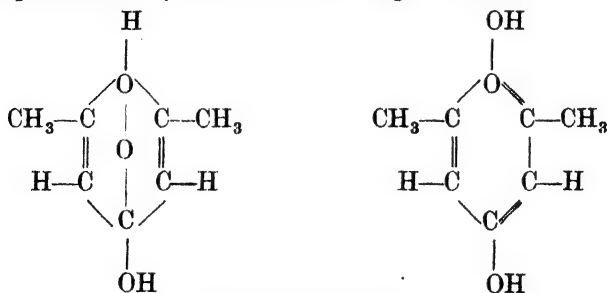
Pinacone change.	Hydrobenzoin change.	Benzilic acid change.	Beckmann change.
		R—CO | CO—R ↓ $+2H_2O$	N—OH ‖ R—C—R ↓ $+H_2O$
R—C(R)—OH | R—C(OH)—R ↓	R—C(H)—OH | R—C(OH)—R ↓	R—C(OH)—OH | HO—C(OH)—R ↓	H—N—OH | R—C(OH)—R ↓
R—C(R)—R | R—C(OH)—OH ↓ $-H_2O$	R—C(H)—R | H—C(OH)—OH ↓ $-H_2O$	R—C(OH)—R | HO—C(OH)—OH ↓ $-H_2O$	H—N—R | R—C(OH)—OH ↓ $-H_2O$
R—C(R)—R | R—CO	R—CH—R | CHO	R—C(OH)—R | COOH	NH—R | R—CO

The fact that all four reactions can be represented in a common system seems to point to the probability that this view of the mechanism may be near the truth ; and it is therefore worth while to examine the matter rather more closely. When we look at the intramolecular rearrangements demanded by this formulation, it is clear that in each case there is a tendency to accumulate hydroxyl radicles upon a single carbon atom instead of allowing them to remain distributed evenly throughout the molecule. Such a grouping is unstable, as is well known ; so that once it is formed it would be liable to break up, and would not be reformed to any extent by a back-reaction.

The conversion[1] of pinacoline alcohol, $(CH_3)_3C.CH(OH).CH_3$, into symmetrical tetramethyl-ethylene, $(CH_3)_2C : C(CH_3)_2$, is evidently another process wherein some intermediate stage must occur; since the direct elimination of water would lead by analogy to some such compound as $(CH_3)_3C . CH : CH_2$. Possibly the course of the reaction is as shown below :—

```
(CH3)2C—CH3            (CH3)2C—OH              (CH3)2C
   |                      |            —H2O        ||
   | /OH      ——→         | /CH3       ——→         ||
   |/                     |/                       ||
CH3—C—H                CH3—C—H                 (CH3)2C
```

The inertness of the carbonyl radicle in certain compounds is very striking; and the rules governing the phenomenon are still unknown, although many of the facts are familiar to first-year students of organic chemistry. The carbonyl groups of carboxylic acids, esters, amides, and imides, seem completely inert so far as the power of forming oximes or hydrazones is concerned. In addition to these well-known cases there are others just as mysterious. For example, diacetylacetone yields a dihydrazone, but the central carbonyl group refuses to react with phenylhydrazine :

$$CH_3 . CO . CH_2 . \mathbf{CO} . CH_2 . CO . CH_3$$

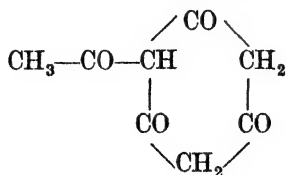
Since the carbonyl groups in the pyrone series show the same reluctance to form oximes or hydrazones, the soundest interpretation of the results is to assume, with Collie,[2] that no true carbonyl radicle is present in diacetylacetone, but that instead it is representable by one of the following structures :

```
            H                                  OH
            |                                  |
           /O\                                /O\
  CH3—C     |    C—CH3              CH3—C         C—CH3
      ||    O    ||                     ||        |
   H—C      |    C—H                 H—C          C—H
       \    C   /                        \   C  //
            |                                |
            OH                               OH
```

Collie's Diacetylacetone Formulae,

---

[1] Zelinski and Zelikow, *Ber.*, 1901, **34**, 3250.

[2] Collie, *J.*, 1904, **85**, 971 : compare Collie, *J.*, 1921, **119**, 1550; Collie and Reilly, 1922, **121**, 1984.

A more difficult case is furnished by aceto-phloroglucinone [1]

which refuses to react with phenylhydrazine despite its four carbonyl groups and notwithstanding the fact that it contains the structure —CO—CH_2—CO— which is usually very reactive. This compound seems well worthy of further investigation in view of its peculiarities.

The characteristics of the carbonyl groups in ketens have already been discussed.

In concluding this chapter it may be well to draw attention to a number of specific cases * which require further investigation. Some of these may be mere examples of polymorphism, but there are others which cannot be accounted for upon any such hypothesis.

From viscosity measurements,[2] it appears that nitrobenzene exists in two different forms, though the spectra of these appear to be identical.[3] There are two forms of *o*-nitrotoluene, *o*-chloro-toluene, *o*-bromotoluene, *o*-toluidine, *o*-chlorophenol,[4] and *o*-chloroaniline.[5] Two forms of benzophenone exist; and numerous other examples are quoted by Knoevenagel.[6]

Two varieties of 4-quinolinic acid appear to have been isolated which form different salts. Dihydroxy-dinaphthol sulphide exists in two forms which differ from each other in the reactivities of the hydroxyl groups and sulphur atoms.[7] A similar case has been observed in 1-chloro-4-nitronaphthalene, wherein the chlorine atoms have quite different activities in

[1] Heller, *Ber.*, 1912, **45**, 418.

* We are indebted to Professor Smiles for some of the following examples.

[2] Mühlenbein, *Ueber die innere Reibung von Nichtelektrolyten*, p. 57.

[3] Crymble, Stewart, and Wright, *Ber.*, 1910, **43**, 1183.

[4] Ostromisslensky, *Zeitsch. physikal. Chem.*, 1906, **57**, 341.

[5] Knoevenagel, *Ber.*, 1907, **40**, 508.

[6] Knoevenagel, *Entwicklung d. Stereochemie zu einer Motostereochemie*, 1907, p. 213.

[7] Henriques, *Ber.*, 1894, **27**, 2993; Christopher and Smiles, *J.*, 1912, **101**, 710; Crymble, Ross, and Smiles, *ibid.*, 1146; Nolan and Smiles, *ibid.*, 1420.

the two varieties. The more complex phenanthrene nucleus exhibits analogous phenomena, for 3-phenanthrylamine [1] exists in two forms each of which gives rise to a characteristic series of salts which on decomposition regenerate the isomer from which they were prepared, although both forms of the parent amine give rise to identical acetyl derivatives.

Enough has now been said to show that even among the simplest problems of organic chemistry there remains, despite all the work of the past fifty years, an extremely fascinating field of inquiry. It is one which especially lends itself to the propounding of hypotheses ; but it should be remembered that unless a hypothesis suggests lines of further research it is in itself likely to be of little value except as a help to the memory in grouping the known facts in a simpler form.

In the study of phenomena, three questions present themselves in succession. What happens ? How does it happen ? Why does it happen ? In organic chemistry we know the answer to the first question in a vast number of cases ; but our replies to the second are by no means so plentiful ; and in the majority of cases we have no means of solving the problem which the third question puts before us.

[1] Werner and Kuntz, *Ber.*, 1901, **34**, 2325.

APPENDIX I

SYNTHESIS OF VITAMIN A

THE synthesis of vitamin A has been approached by several routes and successfully accomplished. The highly unstable nature of the side chain made the building up of this part of the molecule a difficult problem. Much pioneering work had to be done on the chemistry of unsaturated substances and derivatives of β-ionone. In this field the work of Heilbron and his collaborators is outstanding.

In the synthesis of Arens and van Dorp the first stage is the condensation of β-ionone (I.) and methyl γ-bromocrotonate (II.) by a Reformatsky reaction.[1] This yielded the hydroxy ester (III.), which on dehydration with anhydrous oxalic acid was converted into the ester (IV.). After alkaline hydrolysis of the ester the action of methyl-lithium yielded a C_{18} ketone (V.). The final addition of carbon atoms to the side chain was effected by the use of the magnesium bromide of ethoxyacetylene. The acetylenic derivative (VI.) was catalytically reduced to the corresponding ethylenic compound (VII.). The unstable vinyl ether grouping under the influence of hydrochloric acid readily passed over into the aldehyde (VIII.), and this by the loss of the elements of water gave vitamin A aldehyde (IX.). Vitamin A (X.) itself was obtained from the aldehyde by reduction with aluminium-isopropoxide and isopropyl alcohol.

The graphic scheme is:—

[1] Arens and van Dorp, *Nature*, 1946, **157,** 190; *Rec. Trav. chim.*, 1946, **65,** 338; *Nature*, 1947 **160,** 189; Karrer, Jucker and Schick, *Helv. Chim. Acta*, 1946, **29,** 704.

$$\text{(ring: } (CH_3)_2, CH_3\text{)}-CH{=}CH-C(CH_3){=}O \quad + \quad Br-CH_2-CH{=}CH-COOCH_3$$

(I) (II)

Zn + benzene ↓

$$\text{(ring: } (CH_3)_2, CH_3\text{)}-CH{=}CH-C(CH_3)(OH)-CH_2-CH{=}CH-COOCH_3$$

(III)

↓ $-H_2O$

$$\text{(ring: } (CH_3)_2, CH_3\text{)}-CH{=}CH-C(CH_3){=}CH-CH{=}CH-COOCH_3$$

(IV)

↓ (a) hydrolysis (b) $CH_3.Li$

$$\text{(ring: } (CH_3)_2, CH_3\text{)}-CH{=}CH-C(CH_3){=}CH-CH{=}CH-C(CH_3){=}O$$

(V)

↓ $Br.Mg.C{\equiv}C.O.C_2H_5$

$$\text{(ring: } (CH_3)_2, CH_3\text{)}-CH{=}CH-C(CH_3){=}CH-CH{=}CH-C(CH_3)(OH)-C{\equiv}C.O.C_2H_5$$

(VI)

↓ H_2

$$\text{(ring: } (CH_3)_2, CH_3\text{)}-CH{=}CH-C(CH_3){=}CH-CH{=}CH-C(CH_3)(OH)-CH{=}CH.O.C_2H_5$$

(VII)

HCl, H_2O ↓

$$\text{(ring: } C(CH_3)_2\text{, } -CH_3\text{)}-CH=CH-\underset{}{\overset{CH_3}{\overset{|}{C}}}=CH-CH=CH-\underset{\underset{OH}{|}}{\overset{CH_3}{\overset{|}{C}}}-CH_2-\overset{H}{\overset{/}{C}}=O$$

(VIII)

↓ $-H_2O$

$$\text{(ring: } C(CH_3)_2\text{, } -CH_3\text{)}-CH=CH-\overset{CH_3}{\overset{|}{C}}=CH-CH=CH-\overset{CH_3}{\overset{|}{C}}=CH-\overset{H}{\overset{/}{C}}=O$$

(IX)

↓ reduction

$$\text{(ring: } C(CH_3)_2\text{, } -CH_3\text{)}-CH=CH-\overset{CH_3}{\overset{|}{C}}=CH-CH=CH-\overset{CH_3}{\overset{|}{C}}=CH-CH_2OH$$

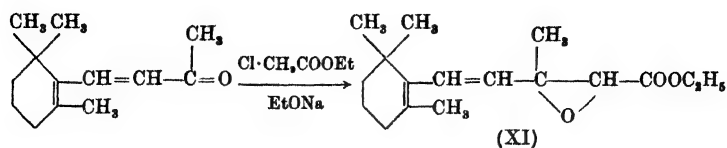
(X), vitamin A

The vitamin has been obtained by another route from β-ionone.[1] The ionone was converted through the glycide ester (XI.) into the aldehyde[2] (XII.), which was then condensed by means of a Grignard reaction with the acetylenic derivative (XIII.) to yield the compound (XIV.). Partial hydrogenation and acetylation gave the hydroxy ester (XV.). This substance on dehydration, presumably through the intermediate compound (XVI.), followed by hydrolysis of the acetate yielded vitamin A (XVII.). The structural steps are:—

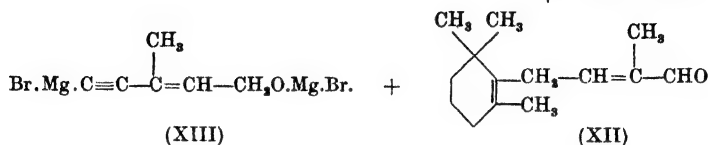
[1] Isler, Huber, Ronco and Kofler, *Helv. Chim. Acta*, 1947, **30**, 1911 ; *Experimentia*, 1946, **2**, 21.

[2] Heilbron, Johnson, Jones and Spinks, *J.C.S.*, 1942, 727 ; Cymerman, Heilbron, Johnson and Jones, *ibid.*, 1944, 141 ; Cymerman, Heilbron and Jones, *ibid.*, 1945, 90 ; Cymerman, Heilbron, Jones and Lacey, *ibid.*, 1946, 500.

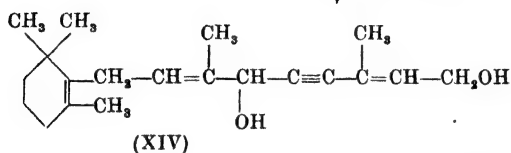
$CH_3\ CH_3$ (ring)—$CH{=}CH{-}C(CH_3){=}O$ (ring—CH_3) $\xrightarrow[\text{EtONa}]{Cl\cdot CH_2COOEt}$ $CH_3\ CH_3$ (ring)—$CH{=}CH{-}C(CH_3){-}CH{-}COOC_2H_5$ (epoxide, O bridging) (ring—CH_3)

(XI)

↓ (a) hydrolysis (b) decarboxylation

$Br.Mg.C{\equiv}C{-}C(CH_3){=}CH{-}CH_2O.Mg.Br.$ + $CH_3\ CH_3$ (ring)—$CH_2{-}CH{=}C(CH_3){-}CHO$ (ring—CH_3)

(XIII) (XII)

↓ (a) Grignard reaction (b) hydrolysis

$CH_3\ CH_3$ (ring)—$CH_2{-}CH{=}C(CH_3){-}CH(OH){-}C{\equiv}C{-}C(CH_3){=}CH{-}CH_2OH$ (ring—CH_3)

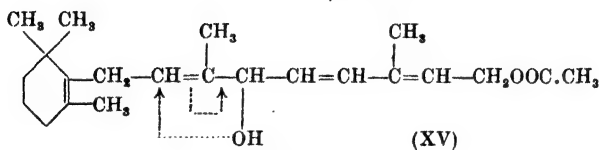
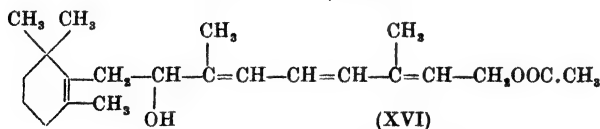
(XIV)

↓ (a) Partial hydrogenation (b) acetylation

$CH_3\ CH_3$ (ring)—$CH_2{-}CH{=}C(CH_3){-}CH(OH){-}CH{=}CH{-}C(CH_3){=}CH{-}CH_2OOC.CH_3$ (ring—CH_3)

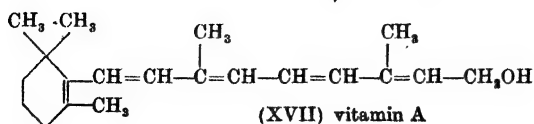
(XV)

intramolecular ↓ change

$CH_3\ CH_3$ (ring)—$CH_2{-}CH(OH){-}C(CH_3){=}CH{-}CH{=}CH{-}C(CH_3){=}CH{-}CH_2OOC.CH_3$ (ring—CH_3)

(XVI)

↓ (a) dehydration (b) hydrolysis

$CH_3\ CH_3$ (ring)—$CH{=}CH{-}C(CH_3){=}CH{-}CH{=}CH{-}C(CH_3){=}CH{-}CH_2OH$ (ring—CH_3)

(XVII) vitamin A

APPENDIX II

FOLIC ACID (PTEROYLGLUTAMIC ACID*)

* Note : The systematic name is,
N[4-{[(2-amino-4-hydroxy-6-pteridyl)methyl]amino}benzoyl] glutamic acid.

1. *Introductory*

This member of the vitamin B group of compounds has recently been examined chemically and synthesised. Biologically active materials from several different sources are now known to owe their properties to pteroylglutamic acid or to derivatives of the acid.

In addition to the relatively simple pteroylglutamic acid (I.), pteroyldiglutamyl-glutamic acid (II.) and pteroylhexaglutamyl-glutamic acid (III.)[1] have been identified.

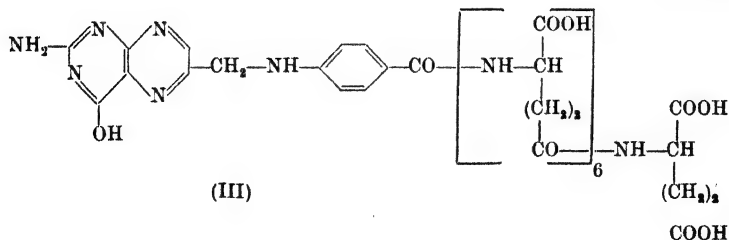
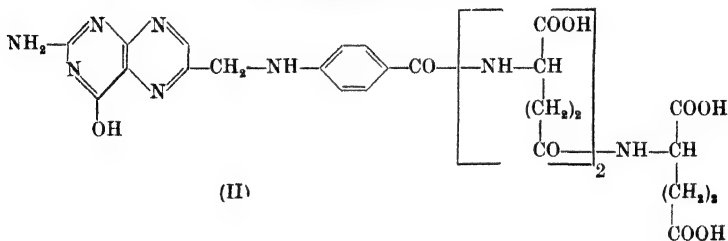
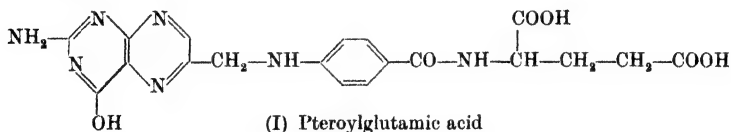
NH_2—(pteridine ring, OH)—CH_2—NH—C_6H_4—CO—NH—CH(COOH)—CH_2—CH_2—COOH

(I) Pteroylglutamic acid

NH_2—(pteridine ring, OH)—CH_2—NH—C_6H_4—CO—[—NH—CH(COOH)—$(CH_2)_2$—CO—]$_2$—NH—CH(COOH)—$(CH_2)_2$—COOH

(II)

NH_2—(pteridine ring, OH)—CH_2—NH—C_6H_4—CO—[—NH—CH(COOH)—$(CH_2)_2$—CO—]$_6$—NH—CH(COOH)—$(CH_2)_2$—COOH

(III)

[1] Pfiffner *et al.*, *Science*, 1945, **102**, 228 ; *J. Amer. Chem. Soc.*, 1946, **68**, 1392.

The growth substances known as liver *Lactobacillus casei* factor, yeast *L. casei* factor and vitamin B_C (isolated from liver) are all identical with pteroylglutamic acid (I.). Fermentation *L. casei* factor from fermentation residues is pteroyldiglutamylglutamic acid (II.) and vitamin B_C conjugate, a product from yeast which corrects vitamin B_C deficiency in chicks, pteroylhexaglutamyl-glutamic acid (III.). A factor from spinach leaves (the original folic acid) and the substance known as vitamin M have not yet been fully identified chemically as pteroylglutamic acid compounds.

2. *The Products of Degradation*

The close connection between the fermentation and liver *L. casei* factors was shown by anaerobic alkaline hydrolysis which broke down the fermentation factor into *dl*-liver *L. casei* factor and two molecular proportions of glutamic acid (IV.).[1] When the fermentation *L. casei* factor was subjected to aerobic alkaline hydrolysis two fractions were obtained in equimolecular amounts. One was identified as 2-amino-4-hydroxypteridine-6-carboxylic acid (V.),[2] and the other gave a positive test for an aromatic amine. From this aromatic amine fraction on acid hydrolysis *p*-aminobenzoic acid (VI.) was isolated.

HOOC—CH(NH_2)—CH_2—CH_2—COOH

(IV)

H_2N—C, N, C, N, C—COOH, CH, C—OH (pteridine ring)

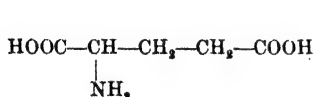
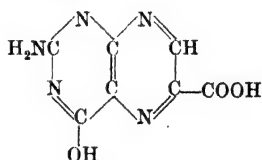
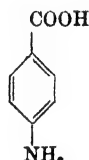
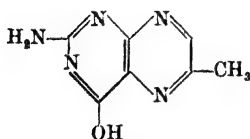
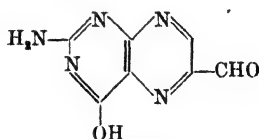
(V)

COOH / benzene ring / NH_2

(VI)

H_2N— (pteridine) —CH_3, OH

(VII)

H_2N— (pteridine) —CHO, OH

(VIII)

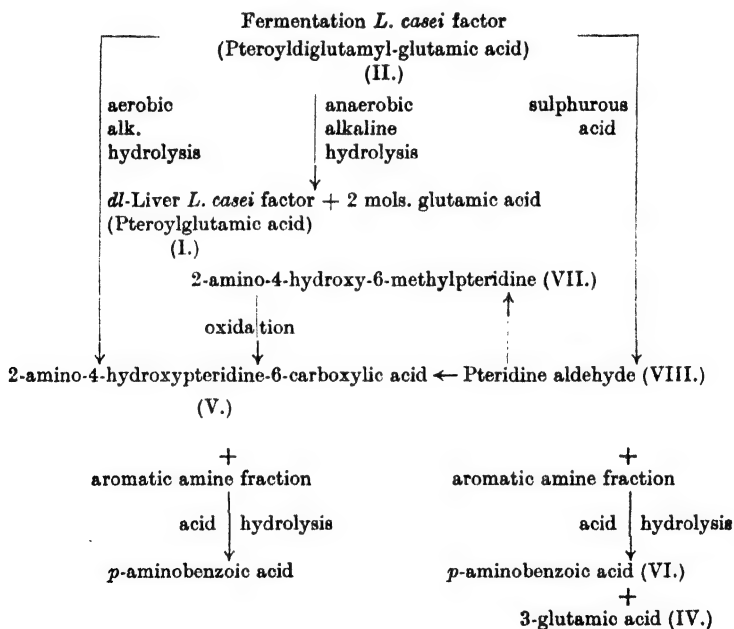
The action of sulphurous acid on the fermentation *L. casei* factor gave two fractions, one a pteridine compound and the other

[1] Angier *et al.*, *Science*, 1945, **102**, 227; 1946, **103**, 667; Pfiffner *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 1476; Stokstad, *J. Biol. Chem.*, 1943, **149**, 573; Hutchings *et al.*, *Science*, 1944, **99**, 371.

[2] Purrmann, *Annalen*, 1941, **548**, 284.

having aromatic amine properties. The pteridine fraction reacted readily with aldehyde reagents, and the aldehyde (VIII.) on standing with dilute alkali in the absence of oxygen through a Cannizzaro-type of change yielded 2-amino-4-hydroxypteridine-6-carboxylic acid (V.) and 2-amino-4-hydroxy-6-methylpteridine (VII.).

Following acid hydrolysis the aromatic amine fraction yielded one molecular proportion of *p*-aminobenzoic acid to three of glutamic acid.

These changes of fermentation *L. casei* factor are shown in diagrammatic form below.

The parallel liberation of aromatic amine and pteridine pointed to the union of the pteridine with the remainder of the molecule through the amine group of the *p*-aminobenzoic acid, and the necessity of oxygen for the alkaline hydrolysis of the factor suggested that the linkage was through a methylene group rather than a carbonyl group. From the nature of the products of hydrolvsis of the amine faction the presence of a peptide linkage

was probable. Taking this evidence into consideration pteroylglutamic acid was given the structure (I.).

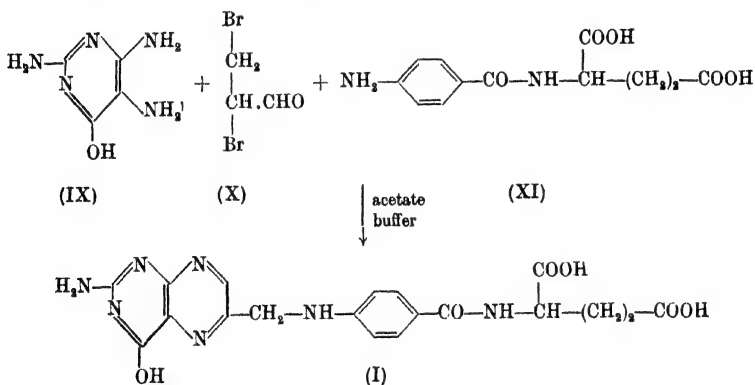
3. *The Synthesis of Pteroylglutamic Acid*

The structure (I.) is supported by two different syntheses. By the first method equimolecular amounts of 2 : 4 : 5-triamino-6-hydroxypyrimidine (IX.), 2 : 3-dibromopropionaldehyde (X.) and *p*-aminobenzoyl-*l*(+)-glutamic acid (XI.) were condensed in the presence of an acetate buffer. The dihydro derivative first formed was oxidized during the course of the reaction to pteroylglutamic acid (I.).

The structural scheme is:—

H_2N, N, NH_2, N, NH_2, OH (IX) + Br–CH_2–CH.CHO–Br (X) + NH_2–C$_6$H$_4$–CO–NH–CH(COOH)–$(CH_2)_2$–COOH (XI)

acetate buffer ↓

H_2N–(pteridine, OH)–CH_2–NH–C$_6$H$_4$–CO–NH–CH(COOH)–$(CH_2)_2$–COOH (I)

In the second synthesis 2 : 3-dibromopropionaldehyde and pyridine were first condensed and the product (XII.) united with 2 : 4 : 5-triamino-6-hydroxypyrimidine (IX) and potassium iodide to give N[(2-amino-4-hydroxy-6-pteridyl) methyl] pyridinium iodide (XIII.). This compound was then allowed to react with *p*-aminobenzoyl-*l*(+)-glutamic acid, and after purification pteroylglutamic acid was isolated.

The structures are:—

H_2N, N, NH_2, N, NH_2, OH (IX) + O : CH–Br.CH–CH_2–N$^+$(pyridine) $\bar{Br}$ (XII) $\xrightarrow{KI}$

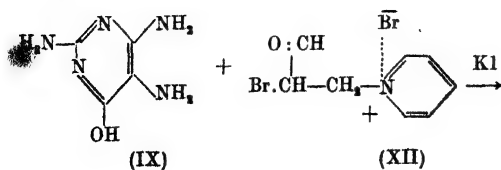
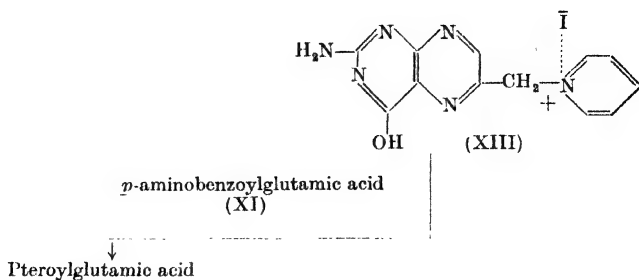
I

H_2N— N N N N —CH_2—N⁺ (pyridinium)

OH (XIII)

p-aminobenzoylglutamic acid
(XI)

↓

Pteroylglutamic acid

These two synthetic compounds were identical in physical and biological properties with the natural substance. The structural connection between the molecules of folic acid and vitamin B_2, and the occurrence of *p*-aminobenzoic acid, another member of the vitamin B group, as part of the folic acid molecule are points of considerable biological interest.

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